Recent Developments in C−H functionalisation of Benzofurans and Benzothiophenes

EurJOC
European Journal of Organic Chemistry

Minireviews
doi.org/10.1002/ejoc.202001470

Special Collection

Recent Developments in C–H functionalisation of Benzofurans and Benzothiophenes

David Morgan,[a] Stephen J. Yarwood,[b] and Graeme Barker*[a]

Benzofurans and benzothiophenes are important pharmaceutical motifs, appearing in a broad range of small molecule therapeutic classes. Often overlooked by synthetic methodologists in favour reactions of the analogous indole bicyclic system, there is nevertheless a plurality of approaches to effecting benzofuran and benzothiophene C–H functionalisations. In this review, we summarise progress in this area over the past five years, including 1) alkylations, 2) arylations and heteroarylations, 3) carboxylations, carbamoylations, and C-heteroatom bond formations and 4) cyclisations.

1. Introduction

Benzofuran and benzothiophene heterocycles are commonly found in pharmaceuticals, as outlined in a 2014 survey of the most common ring systems in drugs listed in the FDA Orange Book.[1] Examples of drugs containing these heterocycles are used in the treatment of various diseases and include antiarrhythmic,[2] anticancer,[3] antifungal,[4] antiasthmatic,[5] and antiosteoporotic,[6] agents as well as others[7] (Figure 1). The bioactivity of benzofurans, their natural sources, and synthetic strategies for assembling the ring system have been recently reviewed by Miao *et al.*, as has the synthesis of benzofuranyl natural products by Heravi and co-workers.[8] Similarly, an overview of benzothiophenes in medicinal chemistry has been presented by Keri and co-workers in a recent review, while Goyal *et al.* have presented a more focussed review of the use of benzofurans as a scaffold for anti-Alzheimer's agents.[9]

A couple of reviews in the past decade have provided an overview of synthetic routes to the benzofuran and benzothiophene ring systems.[10] In 2015, the direct C–H arylation of benzofurans and benzothiophenes amongst other 6,5-fused-heterocycles was highlighted by Guillaumet *et al.*,[11] however to our knowledge the installation of other functionalities has not been reviewed recently. Our interest in the area was sparked by our involvement in developing a series of benzofuranyloxoacetic acid EPAC1-selective activators (lead compound SY009 shown in Figure 1) in which the benzofuranyl 3-substituent was found to have a considerable effect on bioactivity and selectivity.[7]

Benzofurans and benzothiophenes share some chemical properties, most notably their most acidic proton at C2-position has a similar pK_a (33 and 32 in THF respectively).[12] The C3-position of benzofuran is more nucleophilic than benzothiophene.[13] Both of these properties are exploited in the development of new C–H functionalisation methodologies of these bicyclics.

While there are many synthetic routes to benzofurans and benzothiophenes,[14] the direct C–H functionalisation of these heterocycles remains an appealing area of research, as this can be utilised to rapidly produce analogue libraries for structure-activity relationship studies (SAR) during drug development.

Herein, we summarise recent developments in the C–H functionalisation of benzofurans and benzothiophenes over the past 5 years, covering 1) alkylations, 2) (hetero)arylations, 3) C–H functionalisations to form new carbon-heteroatom bonds, and 4) intramolecular cyclisations

2. Alkylation

2.1. Transition Metal Catalysed Alkylations

2.1.1. Transition Metal Catalysed C2-Alkylations

Regioselective C2-alkylation of benzofurans and benzothiophenes through transition metal catalysis has been investigated using a variety of different metals and conditions. Recently, the Ramana group investigated the formyl directed alkylation of 3-formylbenzofurans **1** with acrylates using a ruthenium catalyst (Scheme 1).[15] $RuCl_2(PPh_3)_3$ was used with AgOAc, and K_2CO_3 in toluene at 160 °C for 36 h, affording products in up to 68% yield. Branched alkylated products **2** were obtained when using β-substituted acrylates, whilst linear products **3** were accessed from α-substituted acrylates. Both branched and linear products then underwent concurrent deformylation at the C3-position.

[a] *D. Morgan, Dr. G. Barker*
Institute of Chemical Sciences
Heriot-Watt University
Riccarton, EH14 4AS Edinburgh, UK
E-mail: dm139@hw.ac.uk
Graeme.Barker@hw.ac.uk
http://barkergroup.wordpress.com/
[b] *Dr. S. J. Yarwood*
Institute of Biological Chemistry, Biophysics and Bioengineering
Heriot-Watt University
Riccarton, EH14 4AS Edinburgh, UK
E-mail: S.Yarwood@hw.ac.uk
https://www.yarwoodlab.hw.ac.uk/

Special Collection *Part of the "YourJOC Talents" Special Collection.*

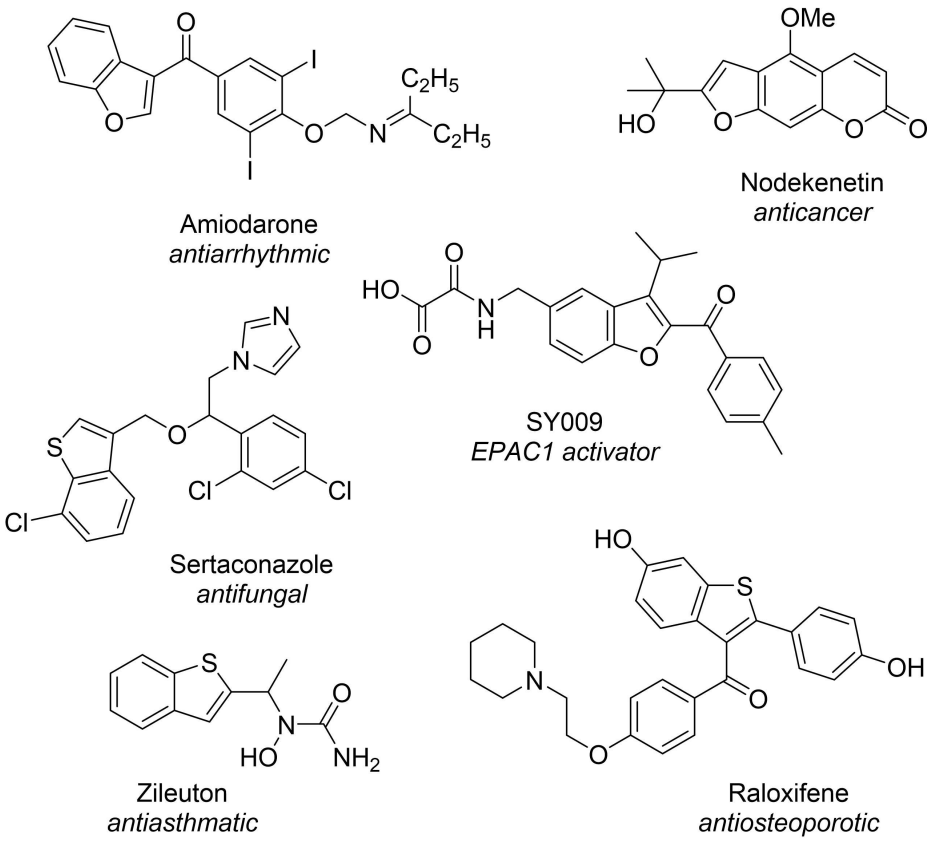


Figure 1. Examples of drugs containing benzofurans or benzothiophenes.

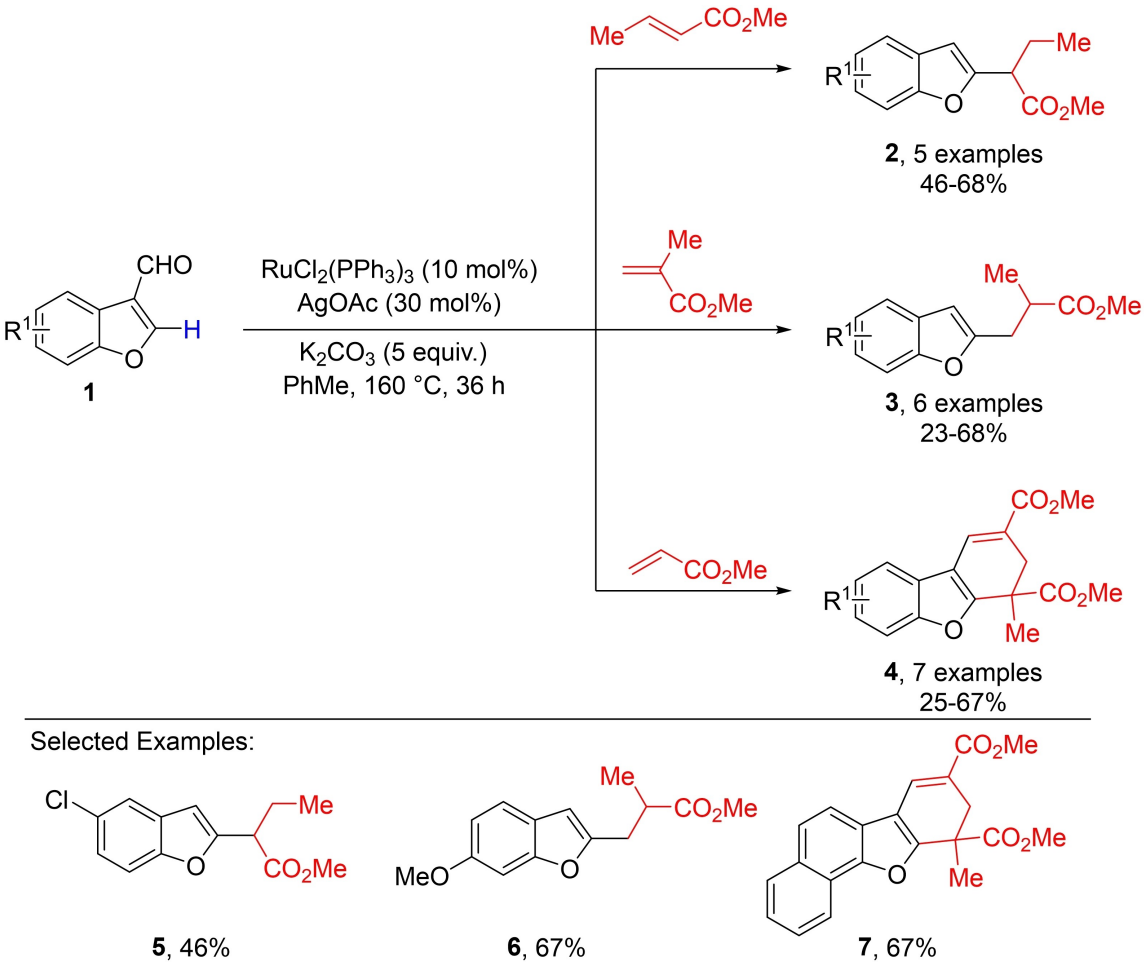
Interestingly, when using methyl acrylate, the addition of another acrylate molecule occurs leading to cycloannulated products **4**. The group investigated the mechanism for this and proposed two possible paths. The first possibility was a Morita–Baylis–Hillman reaction followed by an intramolecular conjugate displacement reaction. The second proposed mechanism was a conjugate addition of the second acrylate molecule, followed by an intramolecular condensation removing the formyl group.

An enantioselective C2-alkylation of *N*-protected 3-aminobenzofurans **8** with α,β-unsaturated 2-acyl imidazoles **9** has been developed by Du and co-workers using a chiral-at-metal

David Morgan graduated with his MChem (Hons.) in chemistry from the University of Hull in 2017, his final year project was under the supervision of Prof. Ross Boyle researching the selective activation of platinum anticancer compounds using phototherapeutic agents. After a year working in industry, David joined the Barker group in 2018 as a Ph.D. student working on the development of small molecule EPAC activity modulators.

Stephen J Yarwood is an Associate Professor in the Institute of Biological Chemistry, Biophysics and Bioengineering (IB3) at Heriot-Watt University (HWU). He obtained his Ph.D. in Biochemistry from the University of Glasgow in 1998. His research interests have been aimed at elucidating the molecular mechanisms underlying inflammatory disease states, like atherosclerosis, which are normally associated with diet-induced obesity and aging. In particular, his research has focused on understanding the mechanisms regulating cAMP signal transduction, particularly the EPAC1/Rap1 signalling system in the control of vascular inflammation.

Graeme Barker obtained his MChem (Hons.) in 2007 from the University of St Andrews and his Ph.D. in 2011 from the University of York, working under the supervision of Prof. Peter O'Brien. He subsequently carried out postdoctoral research at the University of Sheffield in the group of Prof. Iain Coldham, and Heriot-Watt University supervised by Dr. Ai-Lan Lee. He was appointed to an assistant professorship at Heriot-Watt in 2016, where his research interests are divided between C–H functionalisations of common pharmaceutical motifs and medicinal chemistry for modulating cell signalling cascades.



Scheme 1. C2-alkylation of 3-formylbenzofurans.

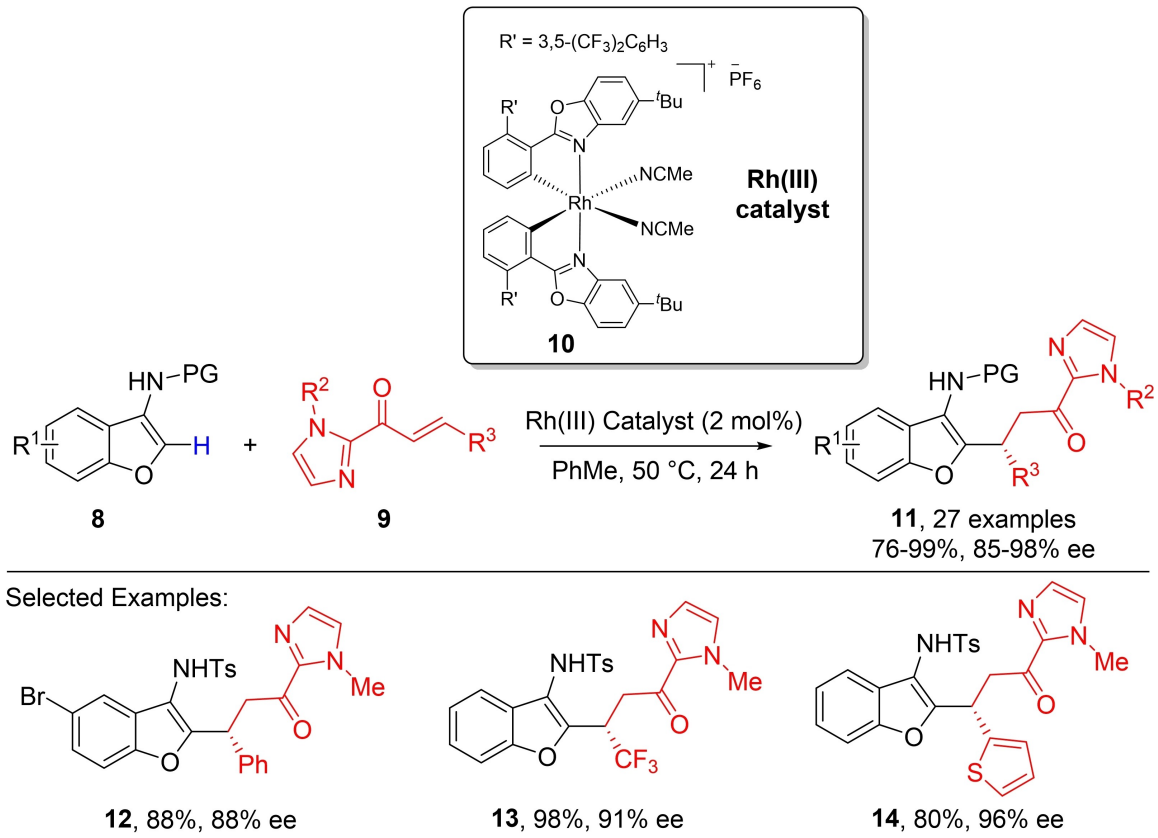
rhodium(III) complex **10** (Scheme 2).[16] Relatively low catalyst loading was required (2 mol%), under mild conditions of 50 °C for 24 h in toluene, giving both high yields (76–99%) and enantioselectivities (85–98%) of products **11**. While *N*-tosylsulfonyl (Ts) was the most commonly used, the reaction was compatible with a range of sulfonamide amine protecting groups including *N*-nitrobenznesulfonyl (Ns) and *N*-methanesulfonyl (Ms). Interestingly the catalyst loading could be reduced further, as 0.5 mol% was used on a gram-scale reaction, resulting in both excellent yield (95%) and enantioselectivity (95% ee).

Additionally, the group reported a single example using these conditions with a 3-aminobenzothiophene substrate **15** to give **16** in 76% yield and 76% ee (Scheme 3).

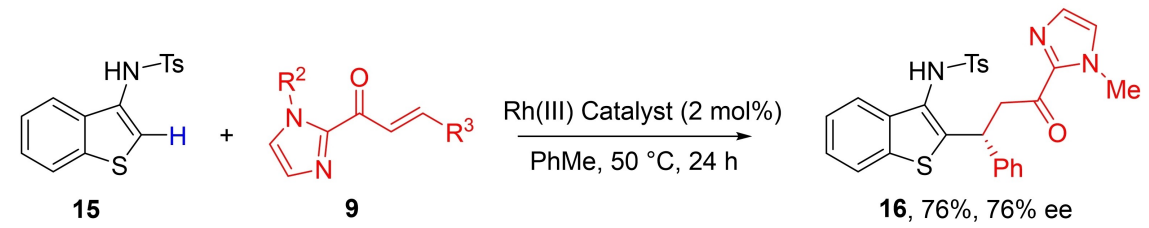
C2-alkylations of benzofurans and benzothiophenes where the C3-position is unsubstituted are more challenging, as regioselectivity issues may arise. In 2017 the Evano group reported the direct C2-alkylation of benzofurans **17** through the copper-catalysed addition of alkyl radicals generated from activated secondary and tertiary alkyl halides **18** (Scheme 4).[17] The reaction preceded using copper (I) iodide with the tridentate ligand tris(2-pyridylmethyl)amine (TPMA) and 2,4,6-collidine in either dioxane or ethanol at 110 °C for 48 h. These conditions were widely applicable, with a broad substrate scope (28 examples) in high yields of products **19** in up to 93%. Unfortunately, when this protocol was applied to benzothiophene substrates it was found to be considerably less efficient with yields of 41–44%, even after attempts at re-optimization.

A similar iron-catalysed radical C2-alkylation of benzofurans with α-bromocarbonyl compounds **23** was reported recently by the Nishikata group.[18] Using iron(II) chloride with *N*,*N*-di-*iso*-propylethylamine as a base in 1,4-dioxane at 110 °C for 24 h, alkylation of a broad scope of benzofurans **24** was obtained (Scheme 5). Although no ligand was required, unfortunately, a large excess of benzofuran was required (3–5 equivalents) for the reaction to proceed with good yields. Both 2-bromoesters and 2-bromoamides were compatible as a source of alkyl radicals. However, the scope was limited to tertiary α-bromocarbonyl compounds, as primary and secondary alkyl radicals were shown to be too unstable for the reaction to proceed in high yields.

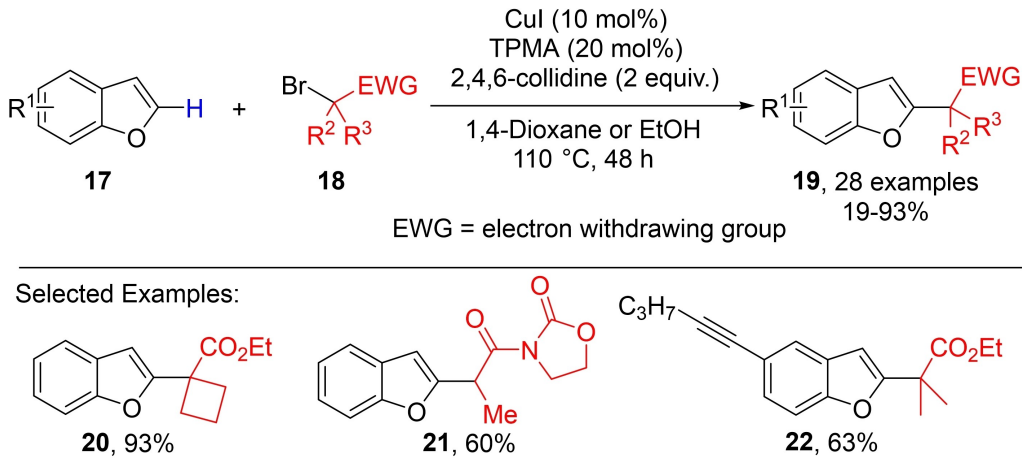
Notably, this procedure is applicable to benzothiophenes giving **30** and **31** in moderate yields of 61% and 57% respectively, although 5 equiv. of ethyl 2-bromo-*iso*-butyrate **29**



Scheme 2. Asymmetric C2-alkylation of C3-substituted benzofurans.

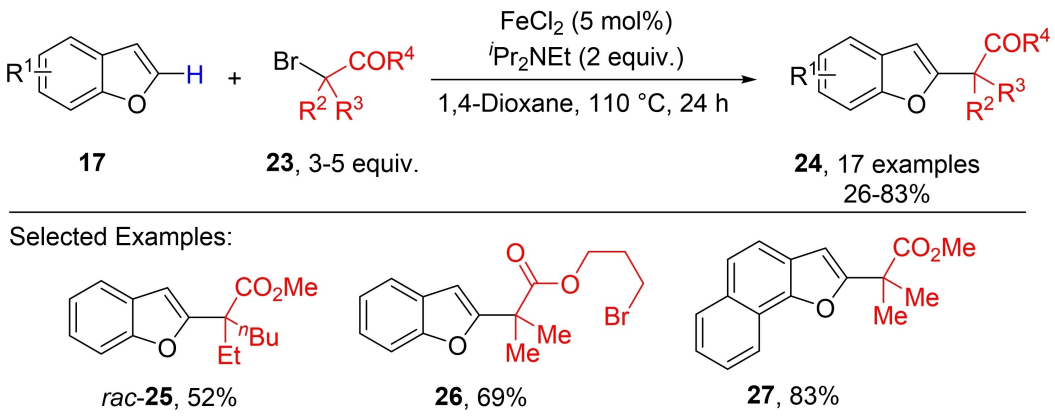


Scheme 3. Asymmetric C2-alkylation of 3-aminobenzothiophene.



Scheme 4. Cu(I)-catalysed radical C2-alkylation of benzofurans with activated alkyl halides.

These are not the final page numbers! ↗↗



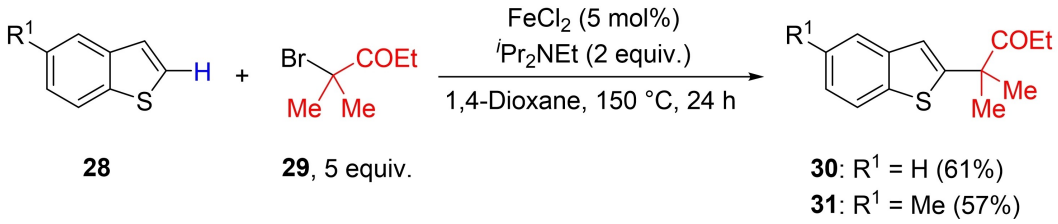
Scheme 5. Fe(II)-catalysed radical C2-alkylation of benzofurans with activated alkyl halides.

and 150 °C was required to push the reactions to acceptable yields (Scheme 6).

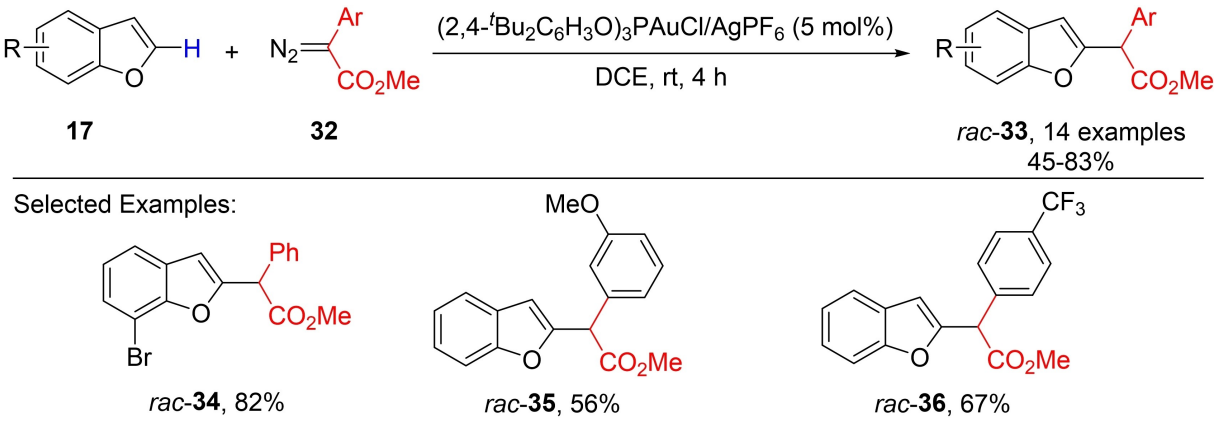
Sun and co-workers have developed a regioselective gold-catalysed C–H alkylation of benzofurans at the C2-position using diazoesters **32** (Scheme 7).[19] This reaction proceeds through the formation of a reactive gold-carbene complex which can be modified to give either C2-alkylated benzofurans **33** or C2-alkylated dearomatised products (i.e. 2-alkyl-1,2-dihydrobenzofurans). For alkylation, a phosphite-gold complex ($(2,4\text{-}^{t}Bu_2C_6H_3O)_3PAuCl/AgPF_6$) was used in dichloroethane (DCE) at room temperature for 4 h on a scope benzofuran substrates, producing decent yields (45–83%) of products **33**. The scope of the reaction was limited to aromatic diazoesters.

Interestingly, 2-methylated benzofuran **37** provided a single example of C3-alkylated product **38**, in a high yield of 78% under the same conditions (Scheme 8).

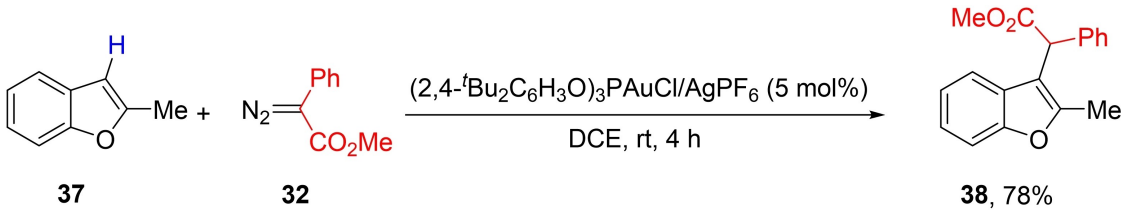
A visible-light photoredox-catalysed decarboxylative alkylation of both benzofurans and benzothiophenes was recently described by Li and co-workers.[20] The Minisci-type transformation was performed through irradiation with blue LEDs in the presence of an iridium-based photosensitizer, as well as a cobalt catalyst to facilitate hydrogen release. 1-Adamantane carboxylic acid was used as the alkylating agent and $n\text{-}Bu_4NOAc$



Scheme 6. Fe(II)-catalysed radical C2-alkylation of benzothiophenes with activated alkyl halides.



Scheme 7. Gold-catalysed C–H alkylation of benzofurans with diazoesters.



Scheme 8. Gold-catalysed C3-alkylation of 2-methylbenzofuran.

as a base. The reaction proceeds in ethyl acetate under mild conditions, giving benzofuran **40** in a 62% yield with C2-selectivity, whilst benzothiophenes **41** and **42** were obtained in 77% and 56% yields, respectively (Scheme 9).

This reaction proceeds without the need for oxidants or any additives, which other groups have previously been required to use in high stoichiometries for similar Minisci-type functionalisations of heterocycles.[21]

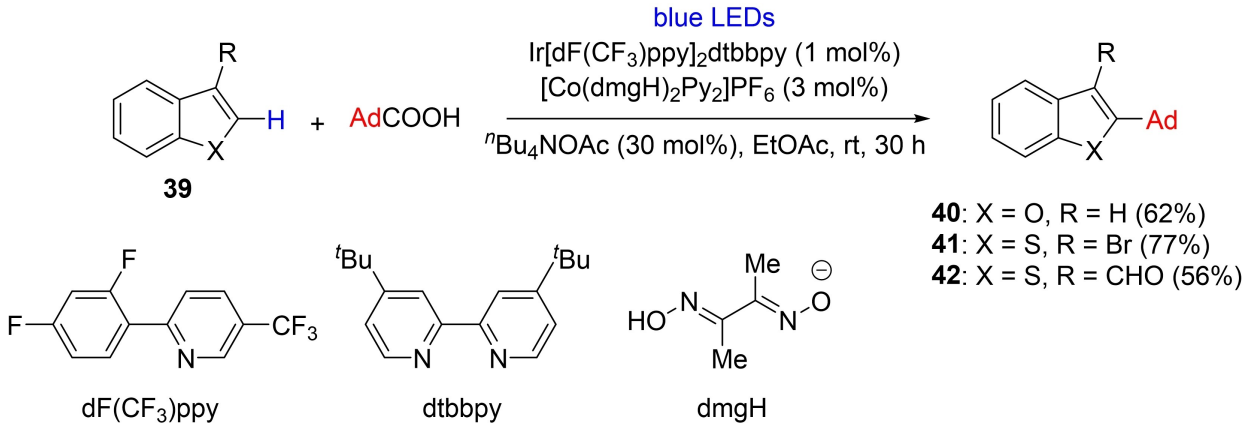
2.1.2. Transition Metal Catalysed C3-alkylations

In contrast to C2 alkylation, transition metal-catalysed C3-alkylations are relatively unexplored, with extant examples limited to specific substrates, or unselective C2/C3 alkylations. The Glorius group[22] have developed a C2-regioselective, non-directed cross dehydrogenative coupling of heteroarenes with alkenes, leading to alkylated products. The reaction proceeded using $[Cp^*RhCl_2]_2$ as the catalyst, with $AgBF_4$, and with the oxidant AgOAc in DCE at 60 °C for 22 h. With (*E*)-prop-1-ene-1,3-diyldibenzene **44** as the allyl substrate, the reaction with unsubstituted benzofuran led to **45** in 50% yield with >20:1 selectivity towards the C2 position, whilst benzothiophene produced **46** in 43% yield although no selectivity for either position was observed (Scheme 10).

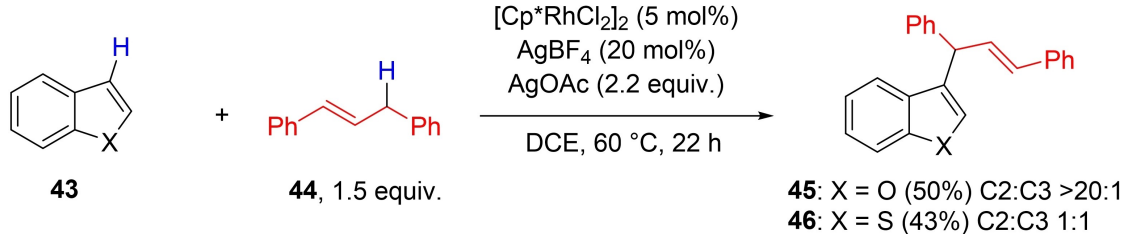
Additionally, allyl benzene **47** was also coupled with benzothiophene and 5-fluorobenzothiophene to give products **48** and **49** in 34% and 37% yields. Although these yields were moderate at best, good selectivity was achieved with 10:1 and >20:1 favoured towards the C3-position (Scheme 11).

2.2. Non-Transition Metal Catalysed Alkylations

Although less common, there are a few examples of non-transition metal alkylations of benzofurans and benzothio-



Scheme 9. Photoredox-catalysed decarboxylative alkylation of benzofurans and benzothiophenes.



Scheme 10. Rhodium-catalysed functionalisation of benzofuran and benzothiophene

Scheme 11. Rhodium-catalysed C3-selective functionalisation of benzothiophenes.

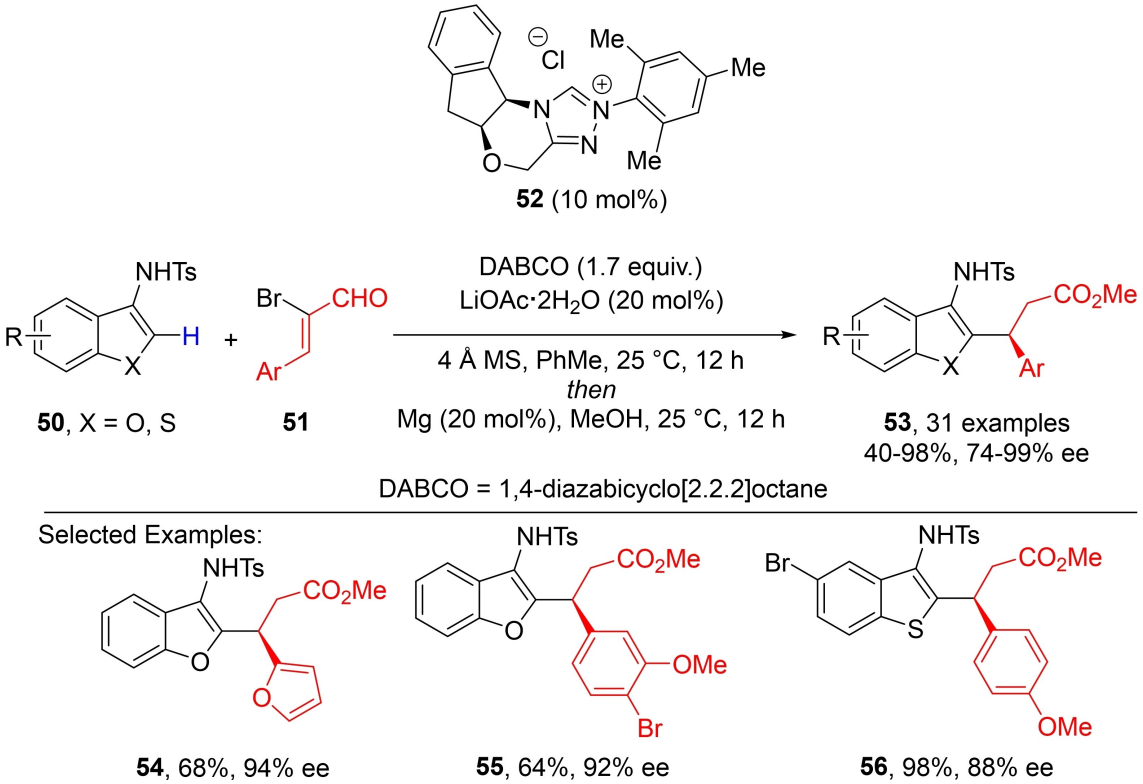
phenes described in the literature, typically by exploiting preliminary reaction of a coupling partner with an adjacent benzofuranyl 3-substituent, or a benzothiophene *S*-oxide.

2.2.1. Non-Transition Metal Catalysed C2-alkylations

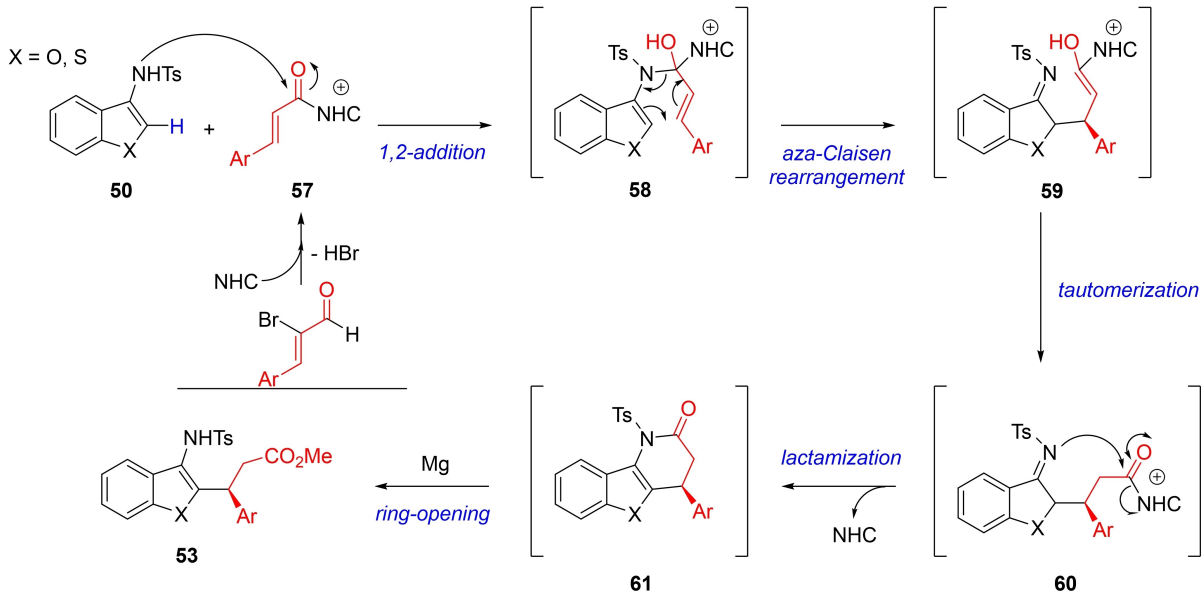
Recently Biju and co-workers reported an *N*-heterocyclic carbene-catalysed enantioselective C2-functionalisation of 3-aminobenzofurans and benzothiophenes **50** using 2-bromoenals **51**.[23] The carbene is generated from chiral triazolium salt **52** using DABCO as a base with LiOAc·2H$_2$O and 4 Å molecular sieves as additives. This is performed in toluene at 25 °C for 12 h. Finally, the addition of catalytic amounts of Mg in methanol at 25 °C for 12 h results in the C2-functionalised heterocycles **53** in yields of 40–98 % (Scheme 12).

The reaction is proposed to proceed *via* the 1,2-addition of the amino heterocycle **50** to the reactive acylazolium intermediate **57** before an aza-Claisen rearrangement to give **59** determines the configuration at the new stereocentre. Tautomerisation of **59** is followed by lactamisation to give the tricycle **61**, which is finally ring-opened using catalytic magnesium in methanol (Scheme 13).

Over recent years, the Proctor group has developed metal-free protocols for the functionalisation of benzothiophene *S*-oxides **62** giving the corresponding substituted benzothiophenes.[24] These interrupted Pummerer rearrangements can be utilised for both C2 and C3-functionalisation.[25]



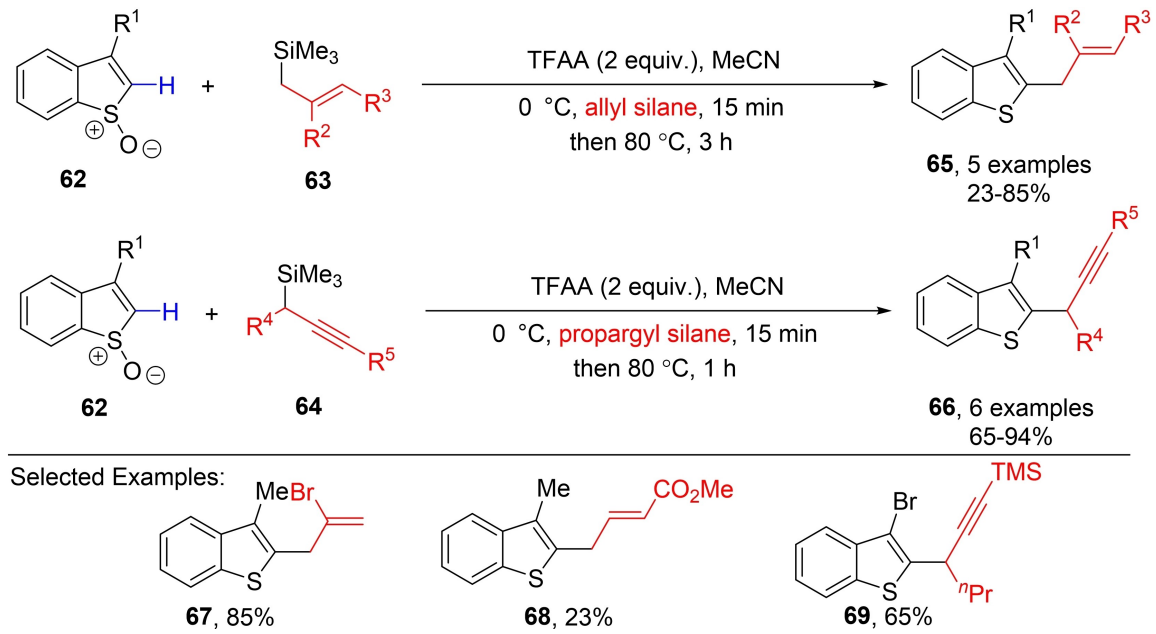
Scheme 12. *N*-heterocyclic carbene-catalysed enantioselective C2-alkylation of 3-amino benzofurans and benzothiophenes.



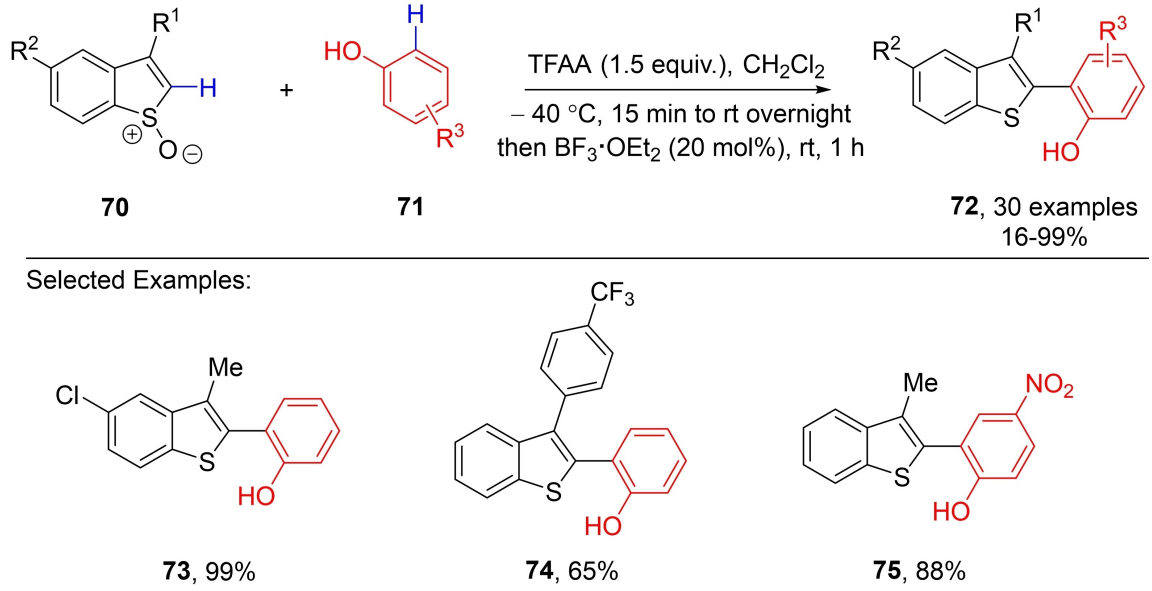
Scheme 13. Mechanism for *N*-heterocyclic carbene-catalysed enantioselective C2-functionalisation of 3-amino benzofurans and benzothiophenes.

In 2018 the group published a protocol for the C2-functionalisation of benzothiophene *S*-oxides **62**,[24a] utilising phenols, or propargyl/allyl silanes to access arylated and alkylated products **65** or **66**. Here, a [1,2]-migration follows the interrupted Pummerer reaction giving complete regiocontrol of the C–C bond formation. Crucially this migration occurred selectively for the newly added group, and there was no migration of the group already installed into the C3 position. C2-alkylation was achieved using trifluoroacetic anhydride in acetonitrile followed by addition of allyl or propargyl coupling partners **63** or **64** at 0 °C, and after being stirred for 15 mins, heated for either 1 or 3 h at 80 °C (Scheme 14).

This methodology was also applicable for arylation; phenols **71** were readily coupled using TFAA to form a polycycle intermediate, then catalytic $BF_3{\cdot}OEt_2$ was used to induce the ring-opening to give the arylated products **72** in up to 99% yields (Scheme 15).



Scheme 14. C2-Alkylation of benzothiophene *S*-oxides using allyl and propargyl silanes.



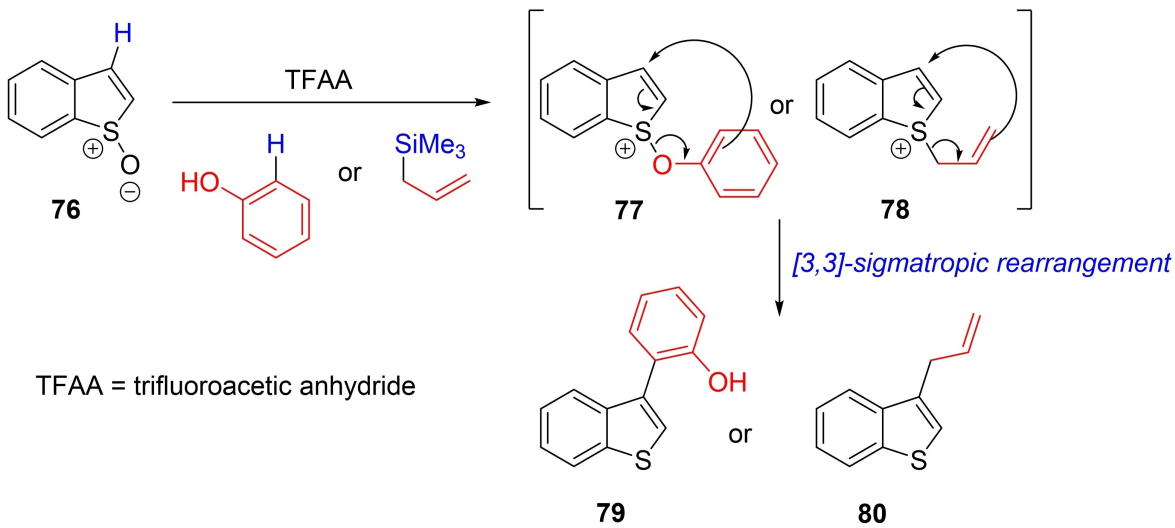
Scheme 15. C2-Arylation of benzothiophene *S*-oxides using phenols.

2.2.2. Non-Transition Metal Catalysed C3-alkylations

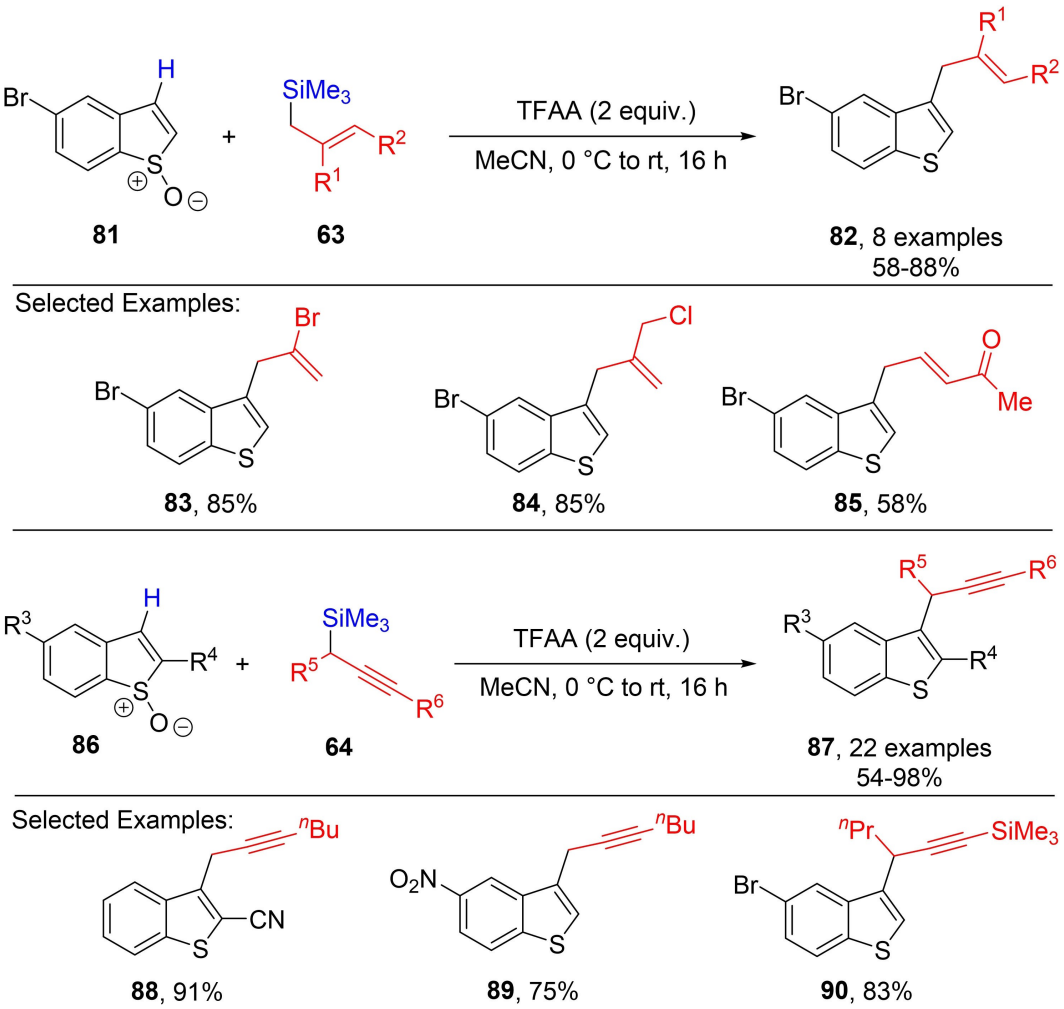
In 2017 the Proctor group investigated the C3-functionalisation of benzothiophene *S*-oxides.[24b] This reaction proceeds by dehydrative or deoxysilylative activation of the S–O bond, before the intermediates **77** or **78** undergo a [3,3]-sigmatropic rearrangement to give the products **79** or **80** with complete regioselectivity (Scheme 16).

First, the C3-alkylation of 5-bromobenzothiophene *S*-oxide **81** was demonstrated using either allyl silanes **63**, with trifluoroacetic anhydride in acetonitrile under mild conditions, giving alkylated products **82** in good yields of 58–88%. Under the same conditions, a range of benzothiophene *S*-oxides **86** underwent alkylation with propargyl silanes **64** to give products **87** in up to 98% yield (Scheme 17).

Additionally, arylation of benzothiophene *S*-oxides **91** was also achieved through coupling with phenols **71** (Scheme 18). These reactions were performed in dichloromethane and heated to 45 °C with *p*-TsOH to ring open the intermediate polycycle **92**. This led to the arylated benzothiophenes **93** in good yields of up to 93%, including steroidal example **96**.



Scheme 16. Simplified reaction mechanism for C3-functionalisation of benzothiophene *S*-oxides.



Scheme 17. C3-Alkylation of benzothiophene *S*-oxides using allyl and propargyl silanes.

3. (Hetero)Arylation

3.1. Transition Metal Catalysed (Hetero)arylations

3.1.1. Transition Metal Catalysed C2-(hetero)arylations

In 2018, Tang and co-workers reported the regioselective palladium-catalysed C2-arylation of benzofurans **17** using *N*′-acyl arylhydrazines **97** as a coupling partner (Scheme 19).[26] The reaction proceeded using a $PdCl_2(MeCN)_2$ catalyst in the absence of a ligand with TEMPO as an oxidant in dioxane heated at 100 °C for 24 h. This resulted in the arylated products **98** in good yields between 57–93 %.

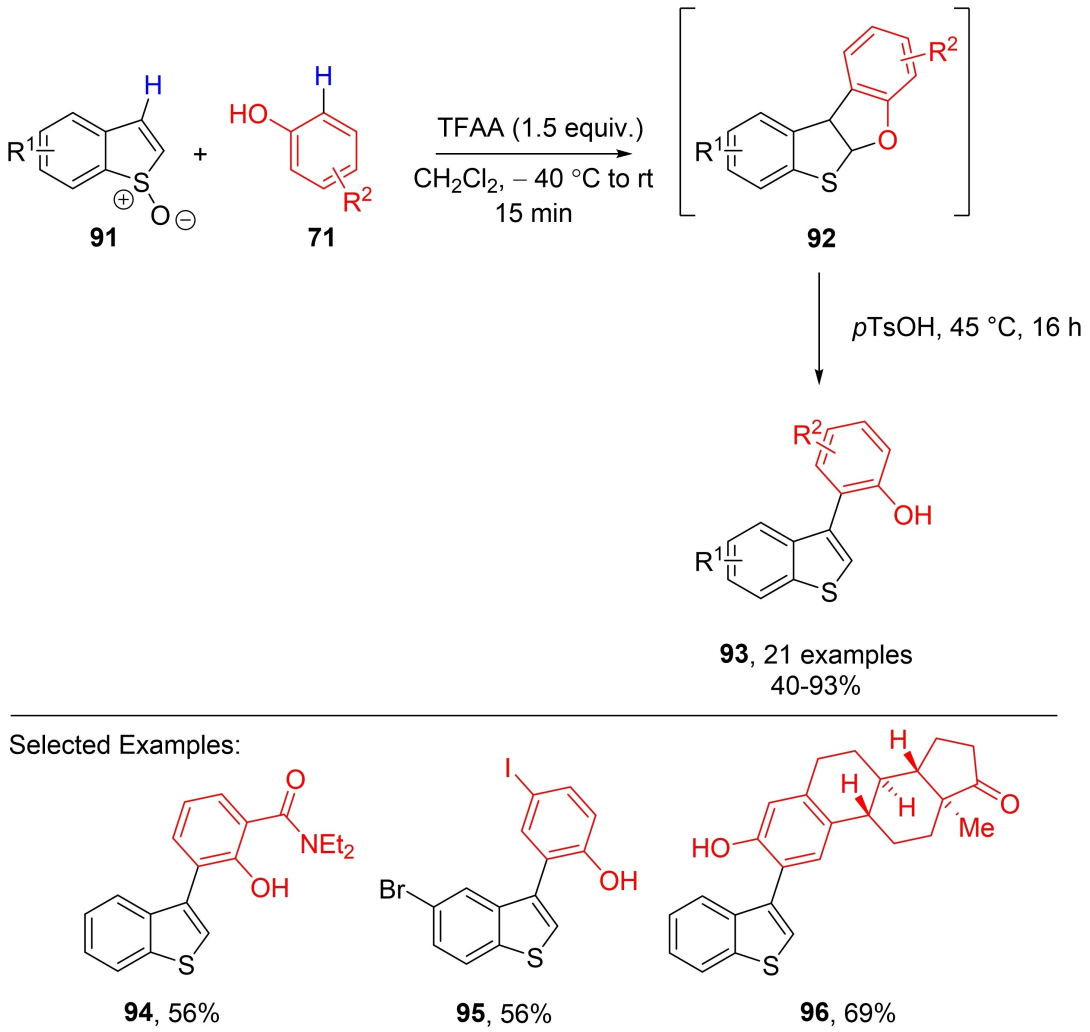
The effect of the acyl group of the arylhydrazines was also investigated, with most examples giving poor yields. However, **103** was produced in 84 % yield when using CF_3 functionalised acylhydrazine **102** with electron-withdrawing nitro group on the phenyl ring, in contrast to only 58 % when using the original acylhydrazine **97** (Scheme 20).

Additionally, the protocol was found to work well on a single benzothiophene substrate **104** giving **106** in a good yield of 73 % (Scheme 21).

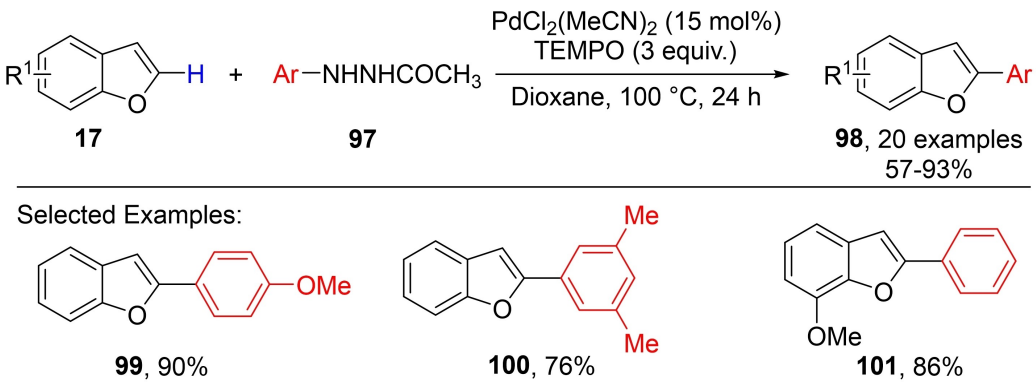
Kapur, Saxena, and Maida reported the palladium catalysed C2-arylation of benzofurans and benzothiophenes with dioxazolones **108** which act as masked ester precursors.[27] The reaction proceeded using $Pd(OAc)_2$ with the oxidant $Cu(OTf)_2$ and KF, under reflux in methanol for 6–10 h. This transformation led to the desired coupled products **109** in moderate yields between 42–65 % (Scheme 22).

The reaction is believed to start through the ring-opening of dioxoazolone **108** to hydroxyimine **114**, before C–H activation to form palladacycle **115**, followed by coordination of benzofuran/benzothiophene **107** to the palladium forming **116**. A 1,2-migration followed by reductive elimination and subsequent hydrolysis results in the formation of arylated heterocycle **117** (Scheme 23).

In 2015 Kuang *et al.* reported the coupling of 1,2,3-triazoles **118** with benzofurans and benzothiophenes using palladium catalysis.[28] $Pd(OAc)_2$ was used with a $AgCO_3$ oxidant and pyridine as an additive. The reaction proceeded in toluene



Scheme 18. C3-Arylation of benzothiophene *S*-oxides using phenols.



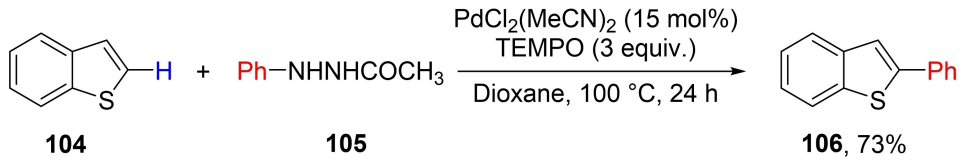
Scheme 19. Pd-catalysed C2-arylation of benzofurans using arylhydrazines.

heated at 90 °C for 18 h, giving the desired products **119** in good yields between 55–71 % (Scheme 24).

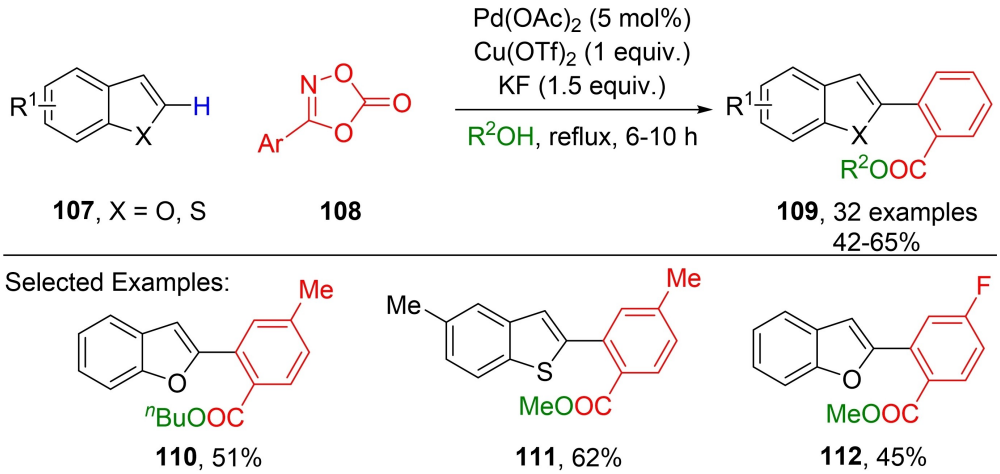
The length of the alkyl chain between the triazole and aromatic groups was also investigated with coupled product **125** produced in a moderate yield of 49 % (Scheme 25).

Doucet *et al.* have recently investigated the coupling of benzofurans and benzothiophenes with various bromopyridines.[29] Benzofuran and benzothiophene were successfully functionalised with 2,6-bromopyridine **126** using Pd $(OAc)_2$ catalyst with a CF_3CO_2K additive heated in DMA at 150 °C

Scheme 20. Pd-catalysed C2-arylation of benzofurans using arylhydrazines with different acyl groups.



Scheme 21. Pd-catalysed C2-arylation of benzothiophene using *N*′-acetylphenylhydrazine.



Scheme 22. Pd-catalysed C2-arylation with dioxazolones.

for 5 hours, giving solely the mono-heteroarylated products **127** and **128** in 85% and 52% yields respectively (Scheme 26).

Products from the subsequent reaction of a second equivalent of benzofuran or benzothiophene could be obtained in one pot through changing base to potassium acetate and increasing the reaction time to 16 h with 2.5 equivalents of benzofuran or benzothiophene. This led to products **129** and **130** being obtained in moderate yields of 62% and 56% (Scheme 27).

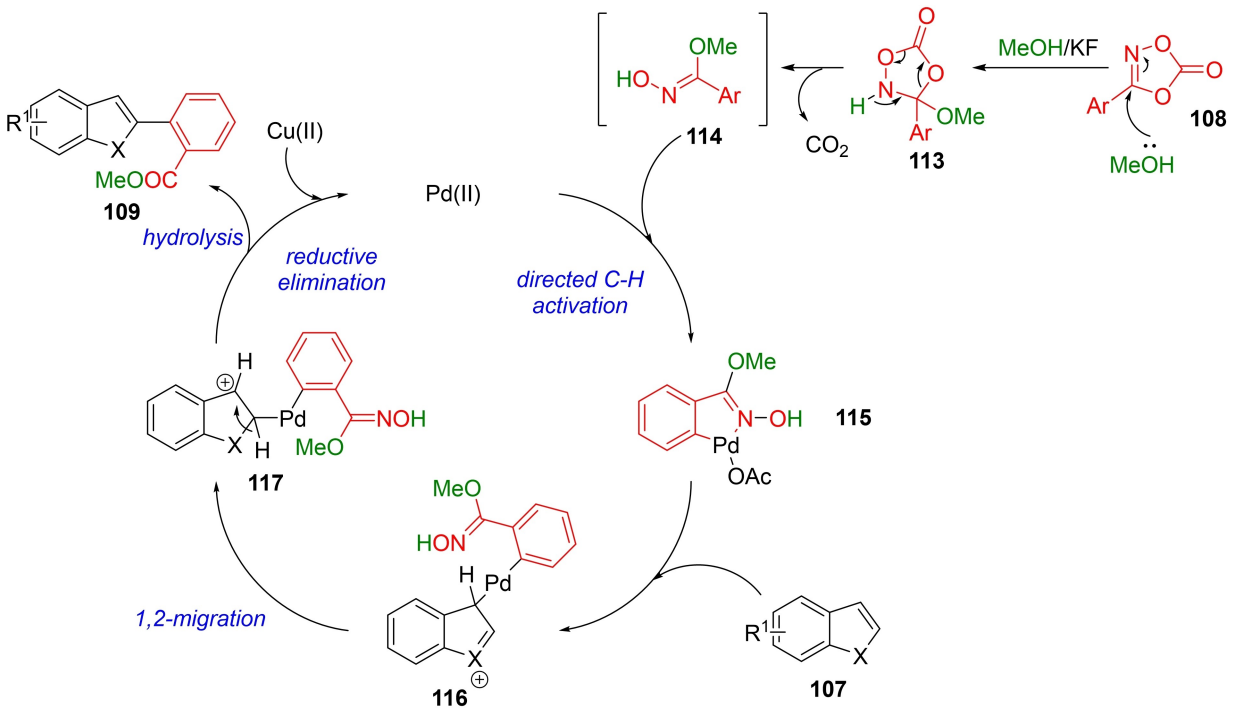
Some other examples of 6-substituted pyridines were also investigated. Under the same conditions for double reaction, 2-bromo-6-(trifluoromethyl)pyridine **131** was heteroarylated to give products **132** and **133** in good yields of 68% and 59% (Scheme 28).

In 2015 Chung reported the sequential C(sp^3)-H and C(sp^2)-H *bis*-arylation of 3-alkylbenzofurans **134** using $Pd(OAc)_2$ with aryl iodides **135** in the presence of tricyclohexylphosphine with silver acetate and pivalic acid.[30] The reaction proceeded under mild conditions, using water as a solvent, and stirring at room temperature for 40 h to give products **136** in up to 90% yield (Scheme 29). No examples of monoarylated products were reported using this methodology.

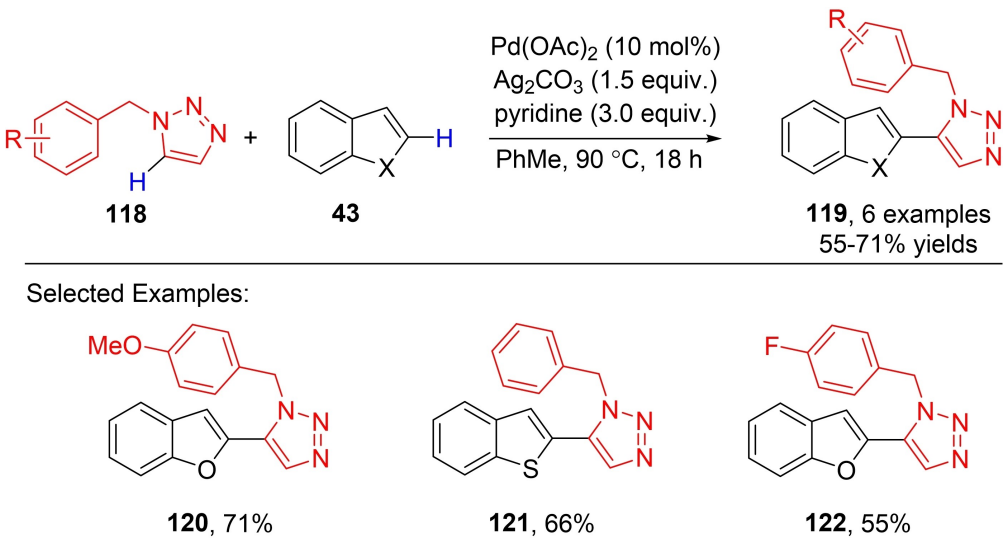
The reaction was regiospecific for the C(sp^3)-H arylation at the 3-position, as seen with the reaction of 3,6-dimethylbenzofuran **140** where **142** was produced in 72% yield (Scheme 30).

The Noël group has recently reported the mild and selective arylation of benzofurans and benzothiophenes using aryldiazonium tetrafluoroborates **143**.[13] While the reaction of benzothiophenes led to 3-arylation, benzofurans were successfully coupled with halogenated aryldiazonium tertrafluoroborates with a low (0.5 mol%) catalyst loading of $Pd(OAc)_2$. Trifluoroacetic acid was added in methanol stirred at room temperature between 30 mins and 16 h, giving the 2-arylated products **144** in good yields of 60–92% (Scheme 31).

You and co-workers recently disclosed the rhodium-catalysed C3-arylation of benzothiophenes **149** through *ortho*-directed C–H activation of 2-pyridyl protected phenols **148**.[31]



Scheme 23. Suggested mechanism for Pd-catalysed C2-arylation reaction.



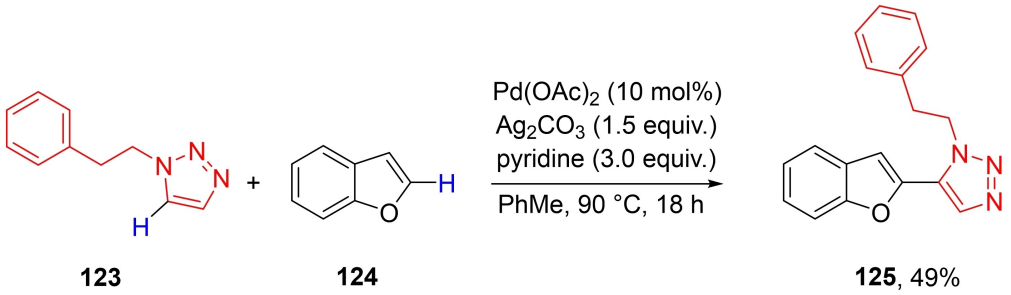
Scheme 24. Pd-catalysed coupling of 1,2,3-triazoles with benzofurans and benzothiophenes.

Using $[Cp^*RhCl_2]_2$ with $AgSbF_6$ and either Cu(OAc)2 or Ag_2O as an oxidant in 1,4-dioxane at either 100 or 150 °C for 24 h a range of coupled products **150** were produced in 43–87% yields including steroidal benzothiophene **151** and indolyl benzothiophene **152** (Scheme 32).

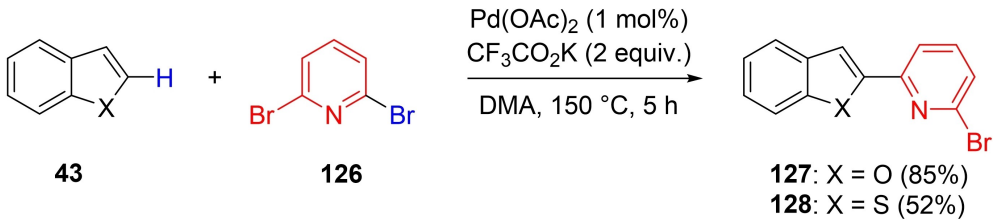
The protocol was extended to a single example of a benzofuran. Under conditions B, benzofuran **154** was obtained in 73% yield (Scheme 33). 2-Pyridyl protected phenols have previously been shown to undergo ready deprotection in high yields.[32]

In 2019, the Gao group described the *ortho*-directed rhodium-catalysed C–H/C–H cross-coupling of benzimidates **155** with both benzofuran and benzothiophenes,[33] this was then followed by elimination of ethanol to give carbonitrile products **156**. The reaction proceeds using the catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ with silver fluoride and potassium acetate in *tert*-BuOH at 100 °C for 24 h, leading to carbonitriles **156** in moderate yields between 37–76% (Scheme 34).

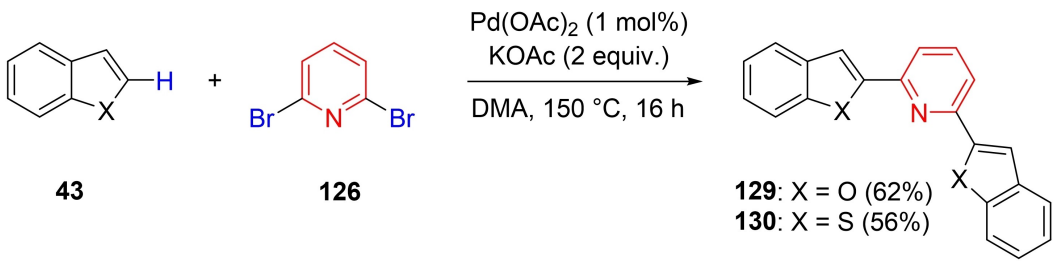
In 2018, You and co-workers reported the iridium-catalysed C2-functionalisation of benzothiophene **104**.[34] When coupling



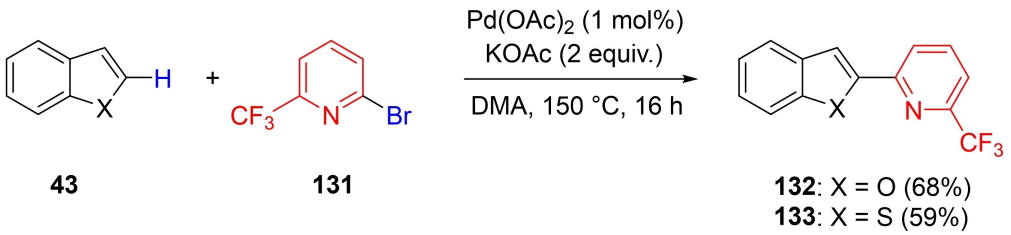
Scheme 25. Coupling of 1,2,3-triazole with extended alkyl chain to benzofuran.



Scheme 26. Pd-catalysed mono-heteroarylation of 2,6-bromopyridine.



Scheme 27. Pd-catalysed di-heteroarylation of 2,6-bromopyridine.

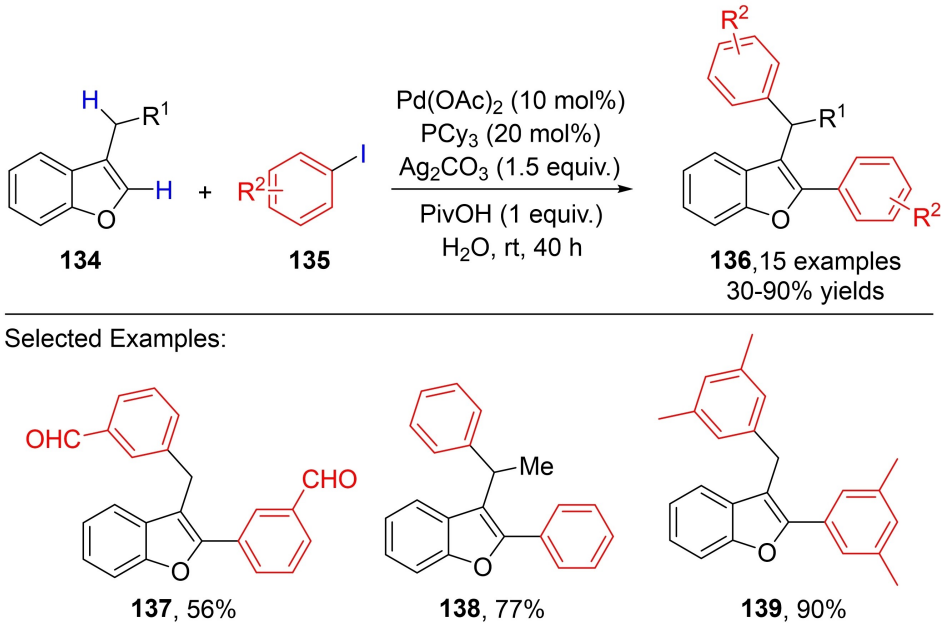


Scheme 28. Pd-catalysed heteroarylation of 2-bromo-6-(trifluoromethyl)pyridines.

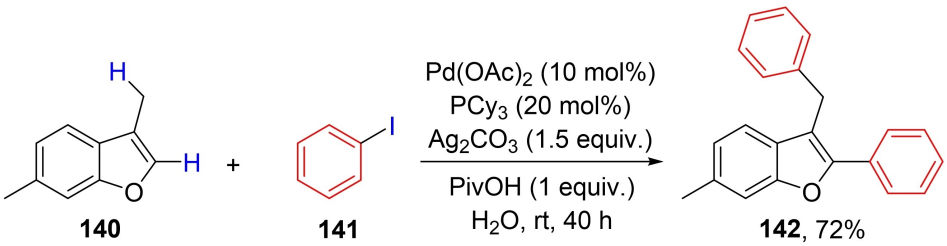
with different functionalised aryl coupling partners **160**, the reaction employed the iridium (III) catalyst $[IrCp^*Cl_2]_2$ with $AgSbF_6$ as a radical scavenger, a Ag_2O oxidant, and a pivalic acid additive in DCE heating at 80 °C for 24 h (Scheme 35). The major drawback to this reaction is the large equivalents of benzothiophene required, although products could be separated from residual benzothiophene using column chromatography. The reaction worked well with a range of weakly and strongly coordinating functional groups including, *N*-methyl-*N*-phenylnitrous amides, pivalanilides, aromatic amides, oxime ethers, and 2-pyrrolidones to give products **161** in 65–95% yields.

Additionally, aromatic ketones **165** could be coupled with benzothiophenes under slightly higher temperatures of 120 °C, giving **166** in moderate yields up to 70% (Scheme 36).

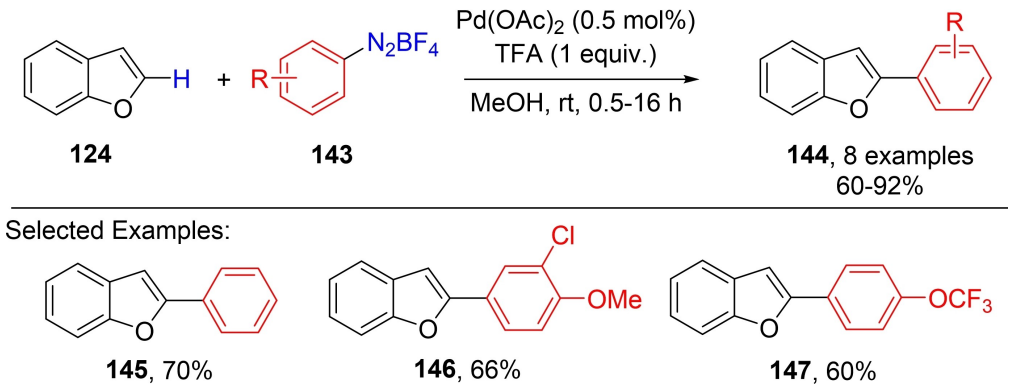
Enamides **167** were also shown to couple with benzothiophenes under this protocol. The vinyl products **168** were formed with exclusive (*Z*)-stereochemistry and in good yields (Scheme 37).



Scheme 29. Bis-arylation of 3-methylbenzofurans.

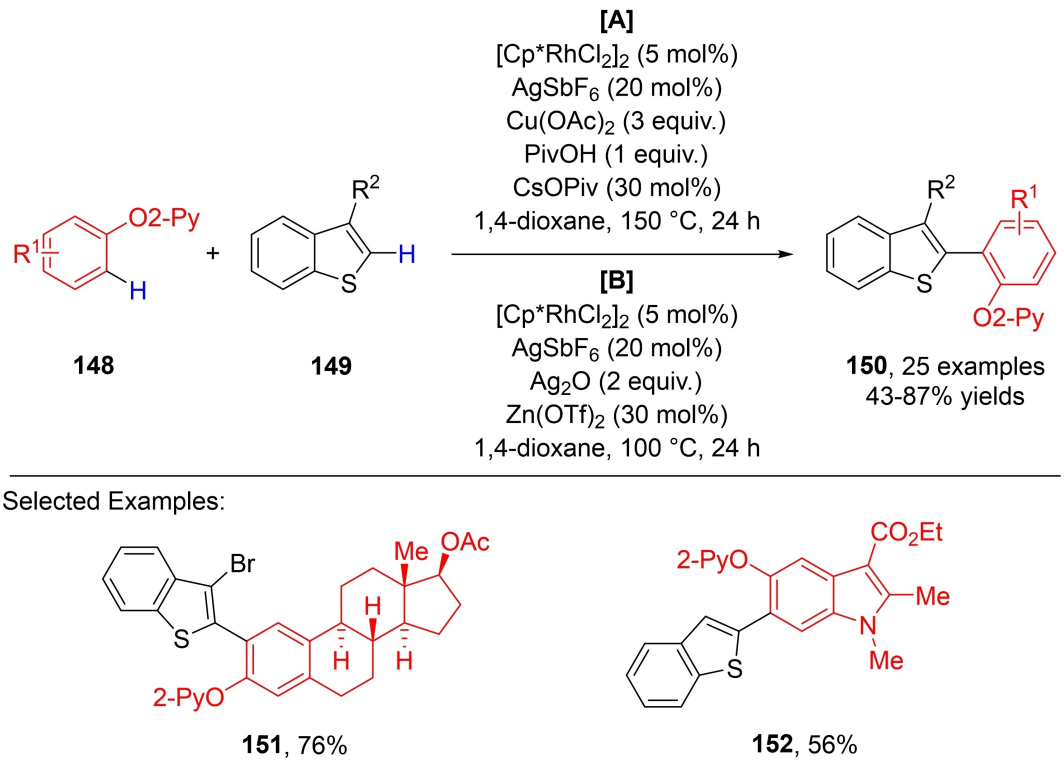


Scheme 30. bis-arylation of 3,6-dimethylbenzofuran

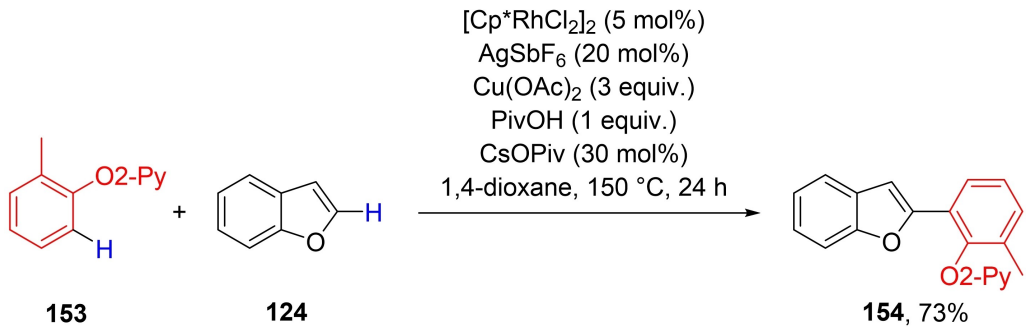


Scheme 31. C2-arylation of benzofurans with aryldiazonium tetrafluoroborates.

C–H arylation of benzofurans and benzothiophenes using earth-abundant (transition) metal systems are less commonly reported, although there are a few recent examples. Canivet and co-workers have developed the Ni-catalysed and Li-mediated arylation of benzothiophenes in the C2 position.[12] The reaction proceeds by coupling benzothiophenes with aryl iodides **135** using $NiCl_2$(bpy) with LiHMDS in dioxane at 120 °C for 16 h (Scheme 38). The reaction is proposed to occur firstly through oxidative addition of Ni(I) to the aryl iodide, followed by transmetallation with the lithiated benzothiophene before reductive elimination of substituted benzothiophene product **173** and regeneration of Ni(I) catalyst. Interestingly, the system



Scheme 32. Rh-catalysed C2-arylation of benzothiophenes.



Scheme 33. Rh-catalysed C2-arylation of benzofuran.

works well in green solvents such as 2-methyltetrahydrofuran (2-MeTHF), cyclopentyl methyl ether (CPME), and anisole, giving good yields of 68%, 74%, and 62% respectively on the model substrates used in optimisation. The catalytic system was broadly tolerant of a range of substitutions and provided a range of functionalised benzothiophenes **173** in up to 94% yields.

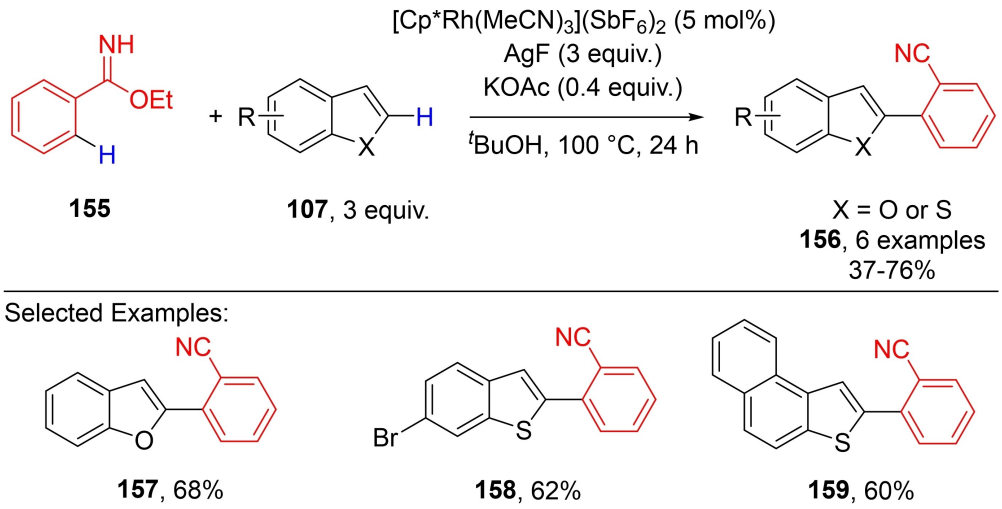
However, when applied to other heterocycles including benzofuran **124**, yields were significantly reduced. Though not fully explained by the authors, this is presumably due to the lower acidity of the benzofuran C-2 proton *vs.* the analogous benzothiophene proton (Scheme 39).

Recently, the Nakamura group have reported the iron-catalysed coupling between benzothiophenes with aryl or alkenyl carboxamides **177** bearing an *N*-(quinoline-8-yl)amide group (Scheme 40).[35] $Fe(acac)_3$ was used with the biphosphine ligand dppen, which was recovered in 89% yield whilst retaining alkene stereochemistry. The organozinc reagent $Zn(CH_2SiMe_3)_2$ is used as a base and 1,2-dichloropropane (DCP) as a relatively mild oxidant. The reaction proceeds in THF at 70 °C for 18 h and the yields of products **178** ranged from 48–92%.

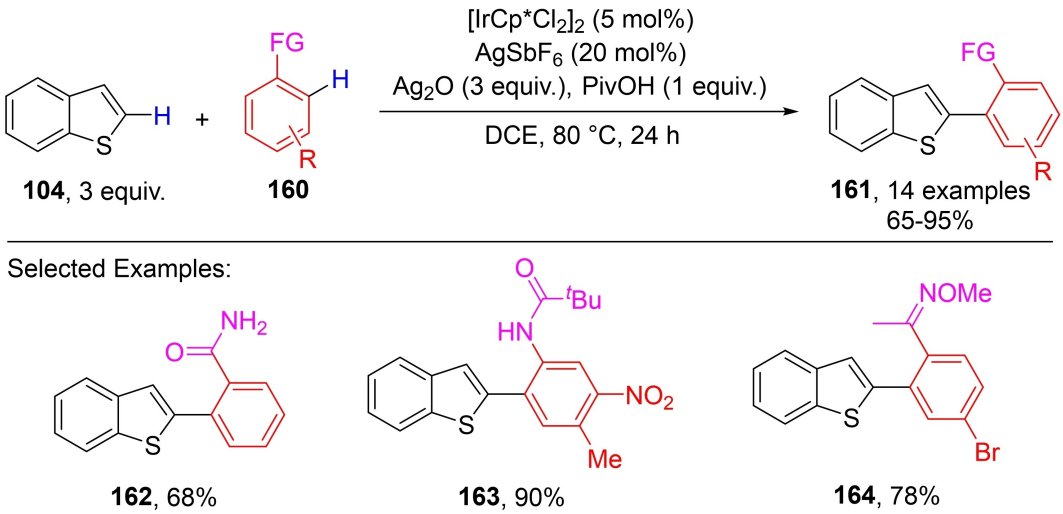
Additionally, a single example of coupling of a benzofuran **124** with a carboxamide **182** was described under the same protocol, giving **183** in 74% yield (Scheme 41).

3.1.2. Transition Metal Catalysed C3-(hetero)arylations

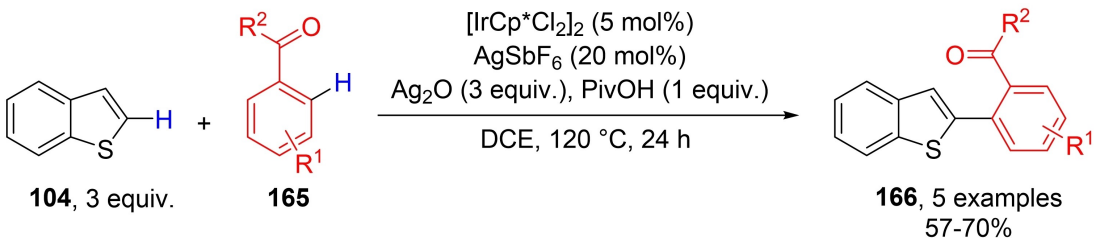
The Noël group found that their previously discussed protocol (Scheme 31) could be extended to benzothiophenes,[13] where a



Scheme 34. C2-arylation of benzofuran/benzothiophenes using benzimidate reagents.



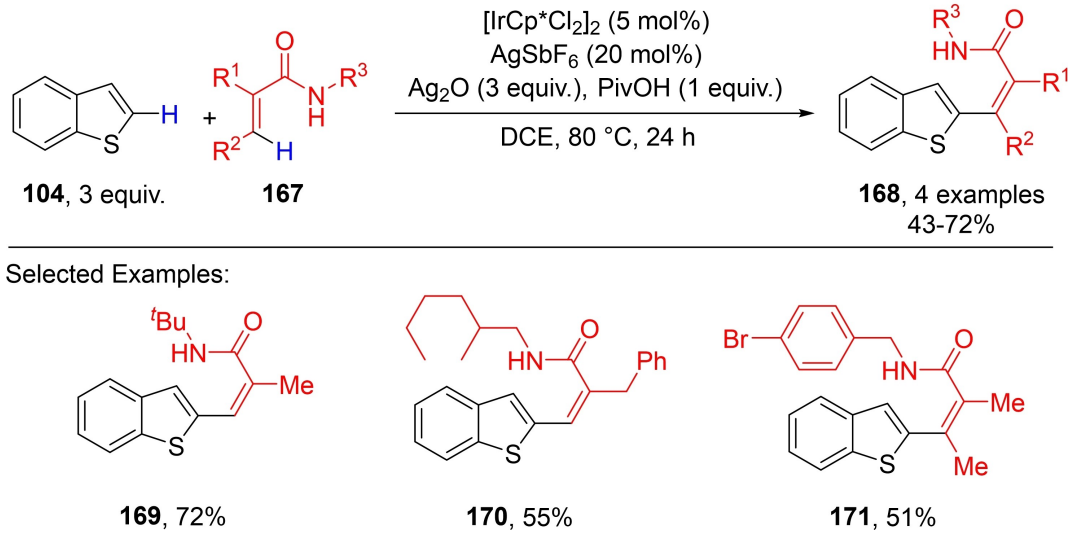
Scheme 35. Ir(III)-catalysed C–H arylation of benzothiophenes.



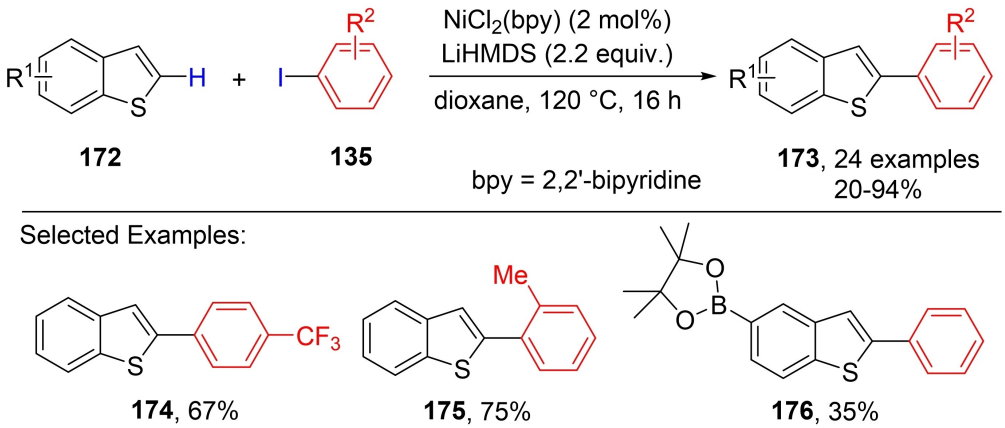
Scheme 36. Ir(III)-catalysed C–H arylation of benzothiophenes using aromatic ketones.

shift in regioselectivity to the C3-position was observed. Due to the lower nucleophilicity of benzothiophene compared to benzofuran, the reaction required a larger catalyst loading of 2 mol%, as well as being heated mildly to 40 °C with now 2 equivalents of aryldiazonium tetrafluoroborate. Products **184** and **185** were obtained in good yields of 80% and 73% as well as excellent regioselectivity (Scheme 42).

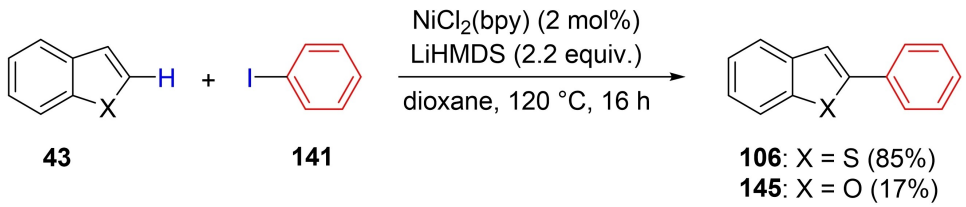
Babu and co-workers have reported the C3-arylation of benzo(thiophene/furan)-2-carboxamides **186** using various aryl and heteroaryl iodides **187** with $Pd(OAc)_2$ and silver acetate.[36]



Scheme 37. Ir(III)-catalysed C–H alkenylation of benzothiophenes using enamides.



Scheme 38. Ni-catalysed Li-mediated C2 arylation of benzothiophenes.

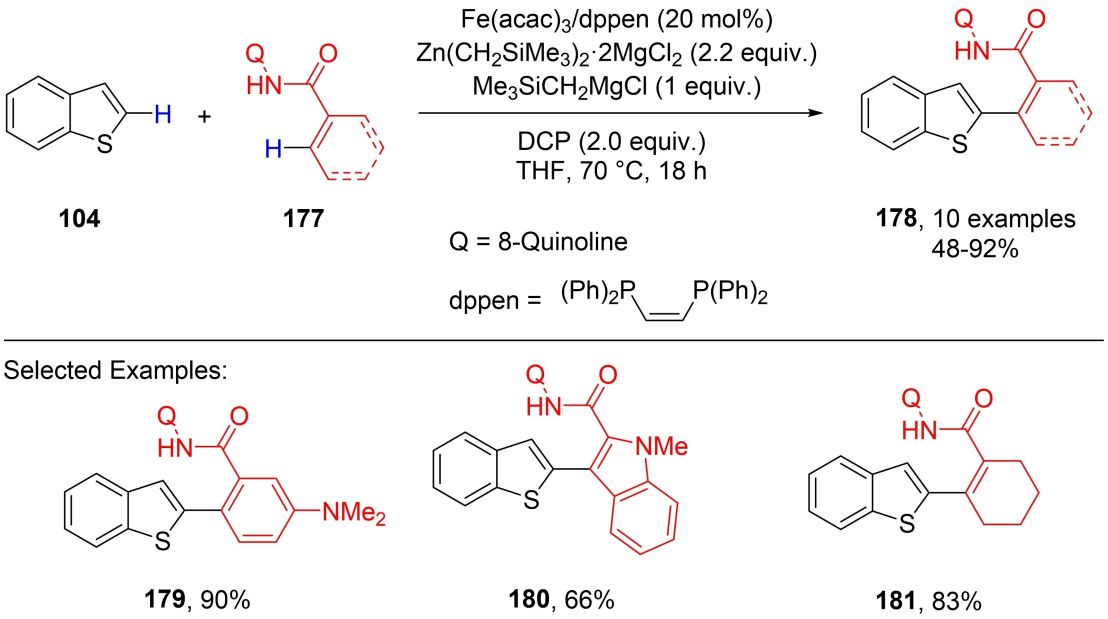


Scheme 39. Ni-catalysed Li-mediated C2 phenylation of benzothiophene and benzofuran.

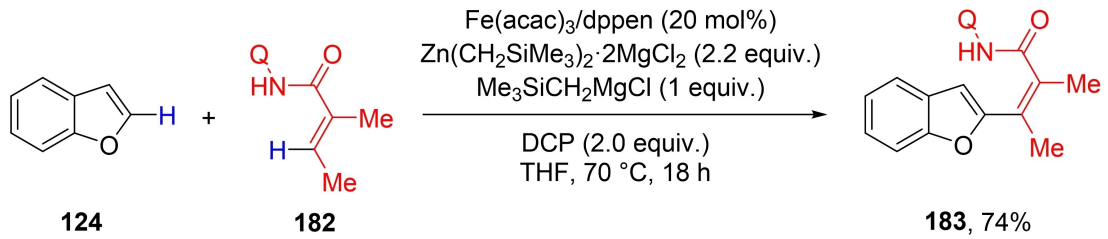
After heating in toluene at 110 °C for 48 hours, products **188** were produced in yields of 16–66% (Scheme 43).

Ramana and Paymode have described a Ru(II)-catalysed carbonyl-directed C3-(hetero)arylation of 2-aroylbenzofurans **192** with either aryl boronic acids, or potassium aryl trifluoroborates.[37] Using $RuCl_2(PPh_3)_3$ as the catalyst, with a potassium carbonate base in toluene, aryl boronic acids were readily coupled at 140 °C in a sealed vial for 24 h and arylated products **193** were obtained in excellent yields between 53–96% (Scheme 44).

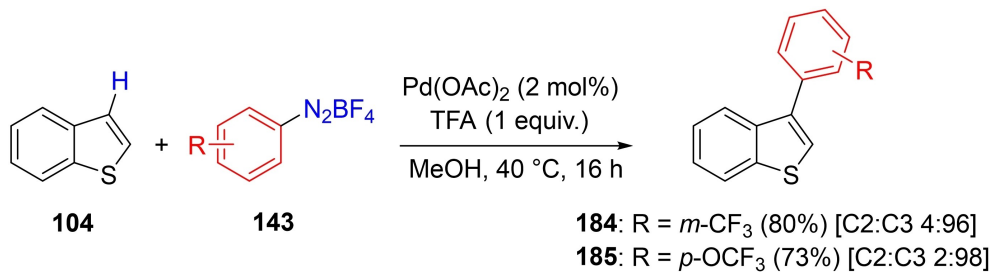
Potassium aryl trifluoroborate salts are more appealing reagents due to their superior stability in non-anhydrous conditions.[38] Higher numbers of equivalents of these reagents were required than when using boronic acids, though under these conditions heteroarylations could also be carried out. The reaction was performed in dichloroethane (DCE) and gave the



Scheme 40. Fe-catalysed coupling of benzothiophenes and aryl and alkenyl carboxamides.



Scheme 41. Fe-catalysed coupling of benzofuran and alkenyl carboxamide.

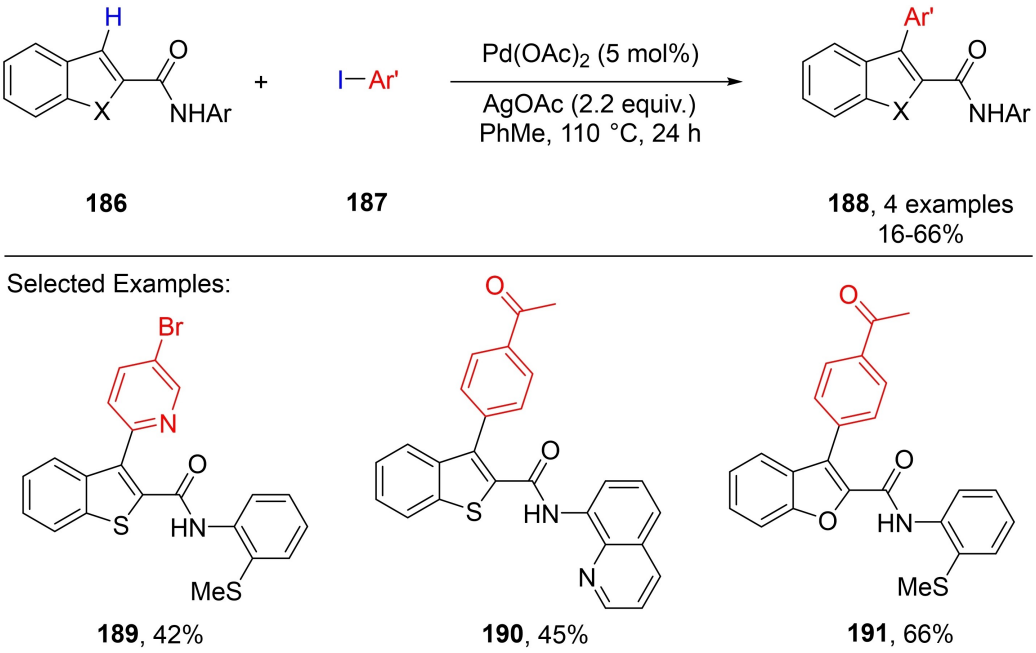


Scheme 42. C3-arylation of benzothiophenes with aryldiazonium tetrafluoroborates.

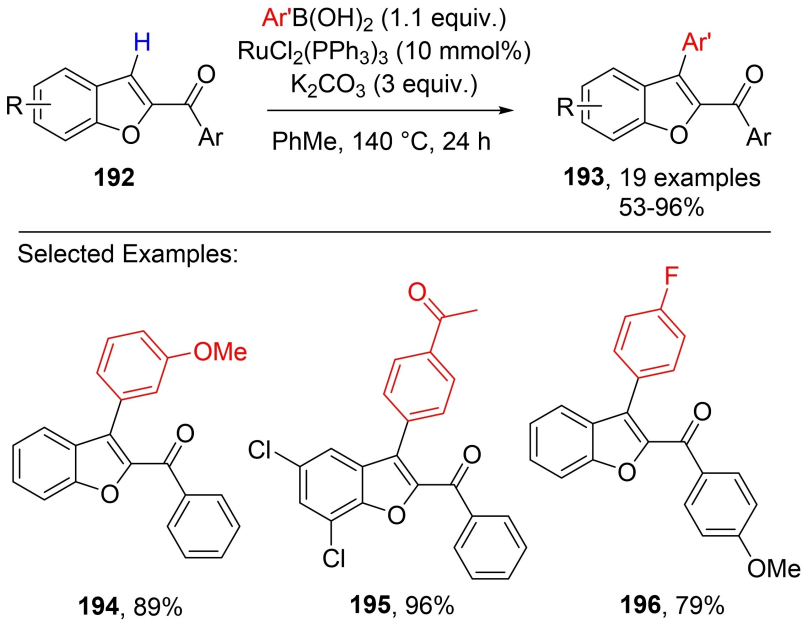
(hetero)arylated products **193** in good yields between 68–83% (Scheme 45).

In 2016, the Lloyd-Jones group utilised gold catalysis under mild conditions in the arylation of a range of heteroarenes with arylsilanes bearing a 3-hydroxypropyldimethylsilyl (HPDMS) group.[39] These aryl-HPDMS reagents were shown to be easily accessible *via* metalation or Rh-catalysis. The gold pre-catalyst thtAuBr$_3$ was used alongside a hypervalent iodine oxidant with camphorsulfonic acid (CSA) in $CHCl_3$ at room temperature for short reaction times (monitored through ^{19}F-NMR). The C2-arylation of 3-bromobenzothiophene **199** was demonstrated in just 17 min, producing **201** in 71% yield (Scheme 46).

C3-arylation of 2-methylbenzothiophene **202** was also demonstrated under slightly different conditions, using PhI(OH)OTs as the oxidant, resulting in **203** in 46% yield in just 10 mins (Scheme 47).



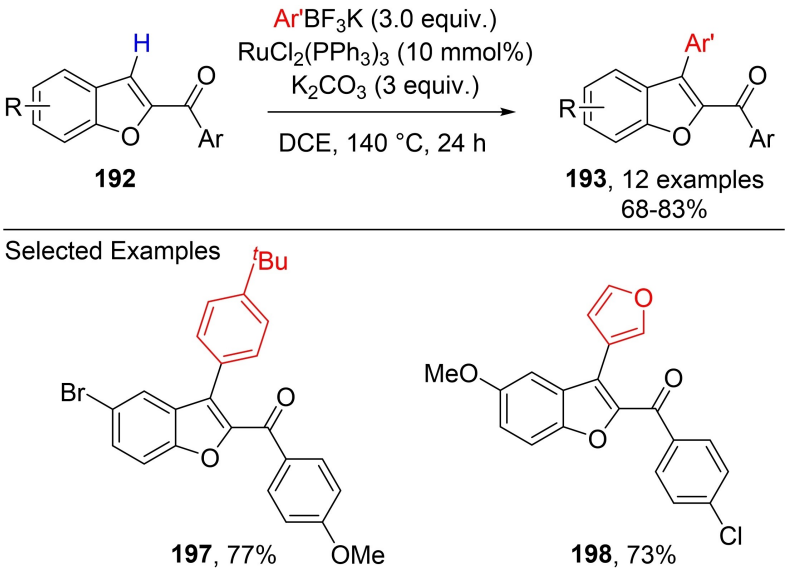
Scheme 43. C–H arylation of benzo(thiophene/furan)-2-carboxamides.



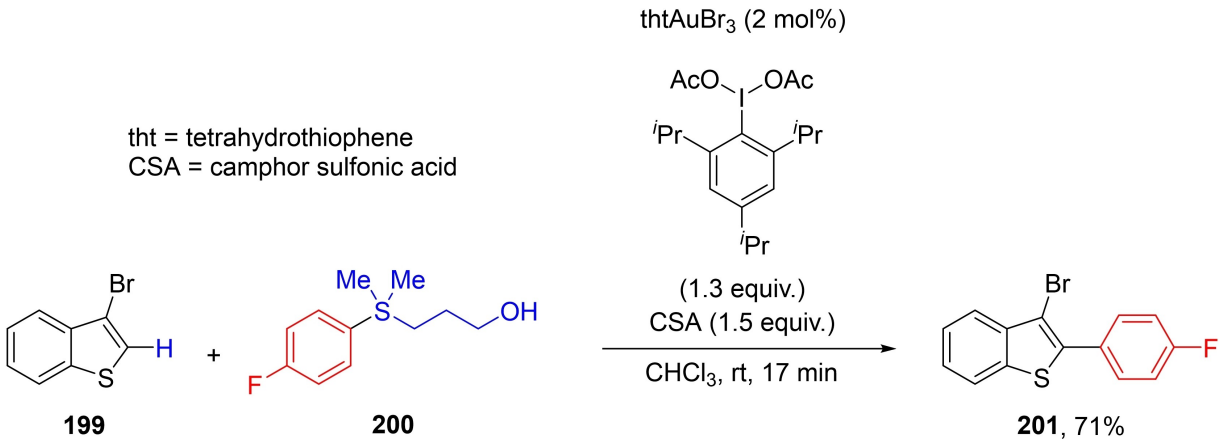
Scheme 44. C3-arylation of benzofurans using aryl boronic acids.

4. Other Functionalisation (Borylation, Phosporylation, Carbamoylation, and Thiolation)

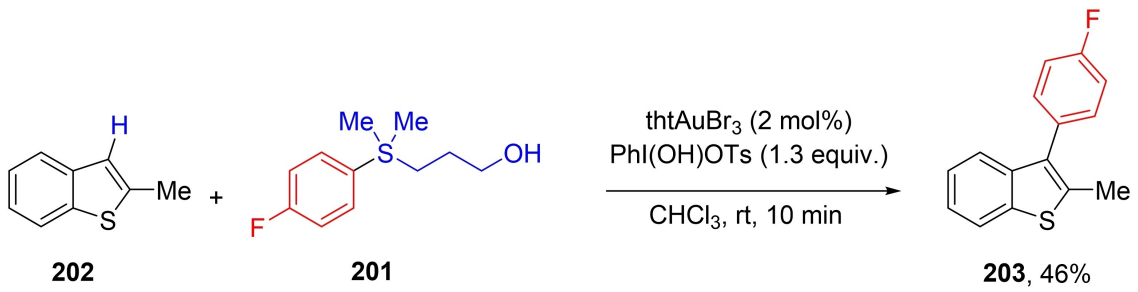
In recent years there have also been a number of reports of benzofurans and benzothiophene functionalisations through carbamoylation or the formation of new C-heteroatom bonds. In 2019, Ito and co-workers described the dimesitylborylation of benzofurans *via* iridium-catalysed C–H activation with silyldimesitylborane **204** (Scheme 48).[40] Here, the Ir(I) pre-catalyst used was $[Ir(Cl)(coe)_2]_2$ with the ligand IMes·HCl/K(O^tBu) in 1,4-dioxane at 120 °C for 24 h, affording the corresponding products **205** in moderate to good yields (55–77%) and completely regioselective for the C2 position. However, a high number of equivalents of the benzofuran derivative was required and a substantial amount of silylated benzofuran side product was formed under the optimal conditions – a 29%



Scheme 45. C3-arylation of benzofurans using potassium aryl trifluoroborates.



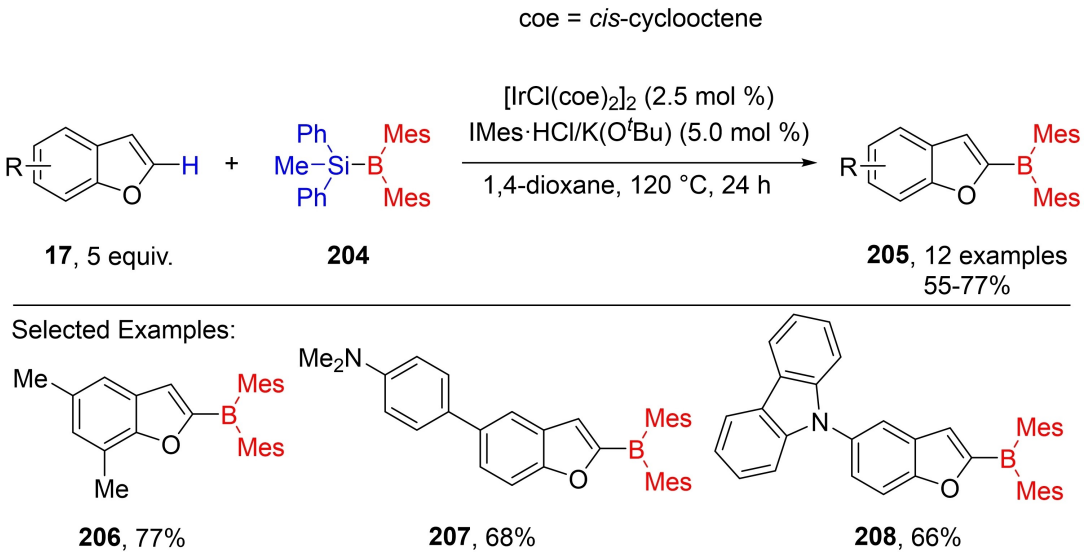
Scheme 46. Au-catalysed C2-arylation of benzothiophene.



Scheme 47. Au-catalysed C3-arylation of benzothiophene.

yield of 2-silylbenzofuran was formed under these conditions when using the parent benzofuran starting material.

The reaction was proposed to proceed *via* preliminary formation of a boryliridum complex, prior to oxidative addition into the benzofuran 2-position C–H bond. Reductive elimination then yielded the product and an iridium hydride; oxidative addition of another equivalent of $Ph_2MeSiB(Mes)_2$ the reductive elimination recycled the boryliridum active catalyst and produced and equivalent of Ph_2MeSiH, the origin of the silylated by-products observed. Interestingly, the reaction of 5-(2-furanyl)



Scheme 48. Ir-catalysed dimesitylborylation of benzofurans.

benzofuran **209** showed complete site selectivity, giving **210** in 55% yield, with no evidence for borylation at the distal furan (Scheme 49).

In 2017, the Cai and co-workers reported the copper catalysed phosphonation of benzofuran and benzothiophene derivatives with trialkyl phosphites **211**.[41] Using a $CuCl_2$ catalyst and $K_2S_2O_8$ as an oxidant in acetonitrile at 100 °C for 12 h, C2-phosphonated products **XX** were obtained in good to excellent yields up to 88% (Scheme 50).

C3-Phosphonation is also possible under these conditions when the C2-position is blocked. A range of benzofuran and benzothiophene substrates **216** were investigated, giving moderate to good yields of **217** in 32–70% (Scheme 51).

The Glorius group has reported the phenylthiolation of benzofurans and benzothiophenes using a recoverable heterogeneous catalytic system involving Pd/Al_2O_3 in the presence of $CuCl_2$.[42] The reaction utilises diaryl disulfides as the sulfur source and is performed in toluene at 130 °C for 16 h. Under these conditions benzothiophenes **28** were found to be selectively functionalised at the C3-position to give moderate yields of products **222** between 27–63% with respect to SAr (Scheme 52).

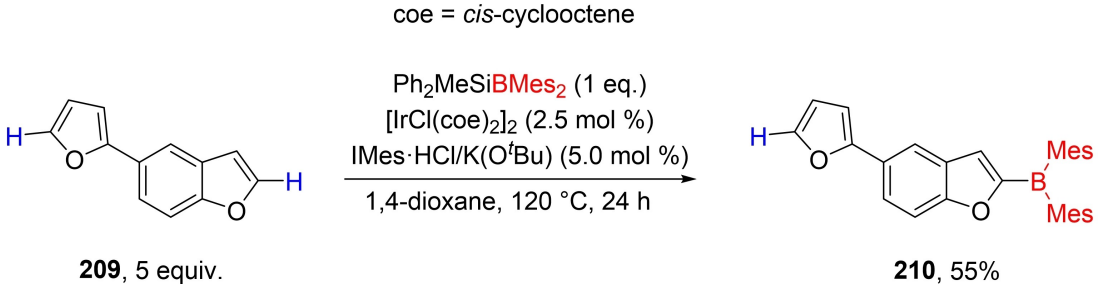
Alternatively, benzofurans showed a preference for phenylthiolation at the C2-position and in less impressive yields of **227** between 29–37% (Scheme 53).

Remarkably, when the C2-position was blocked, C3-functionalisation of a benzofuran was achieved under the same conditions, giving **233** in quantitative yield (Scheme 54).

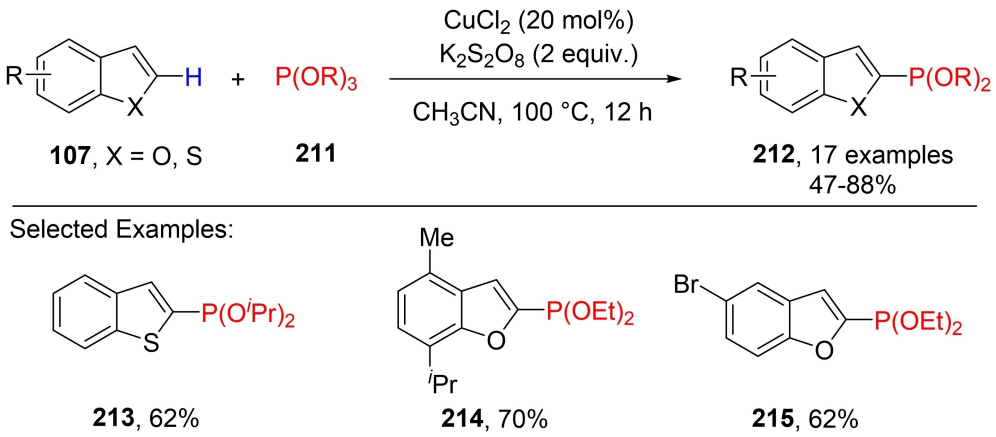
Additionally, when using diaryldiselenide reagents **234** under these conditions with benzothiophene, the selenated products **235** and **236** were obtained in 54% and 48% yields respectively (Scheme 55).

In 2016, Lu and co-workers developed the potassium iodide promoted phenylthiolation of benzofurans using aryl sulfonyl chlorides **238** as the sulfur source.[43] The C3-phenylthiolation proceeded in ethanol at 90 °C for 12 h leading to the products **239** in good yields up to 96% (Scheme 56).

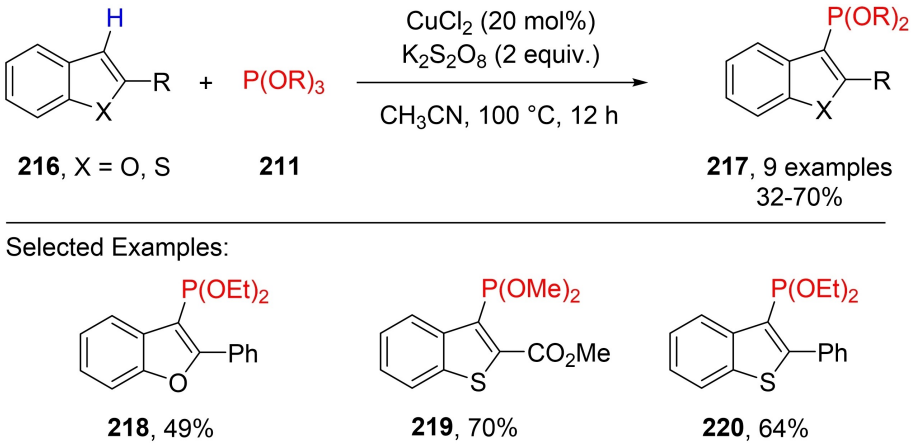
C2-phenylthiolation was also possible using more equivalents of potassium iodide, at the higher temperature of 100 °C for 24 h, giving products **244** in up to 86% yield (Scheme 57).



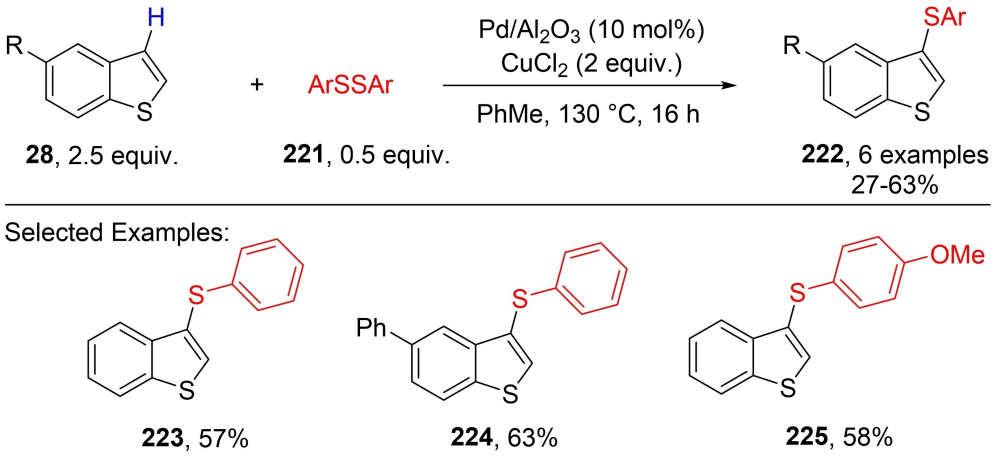
Scheme 49. Benzofuran selective Ir-catalysed C–H dimesitylborylation. Yield determined by NMR with 1,1,2,2-tetrachloroethane as internal standard. Isolated yield in parentheses.



Scheme 50. Cu-catalysed C2-phosphonation of benzofurans and benzothiophenes.

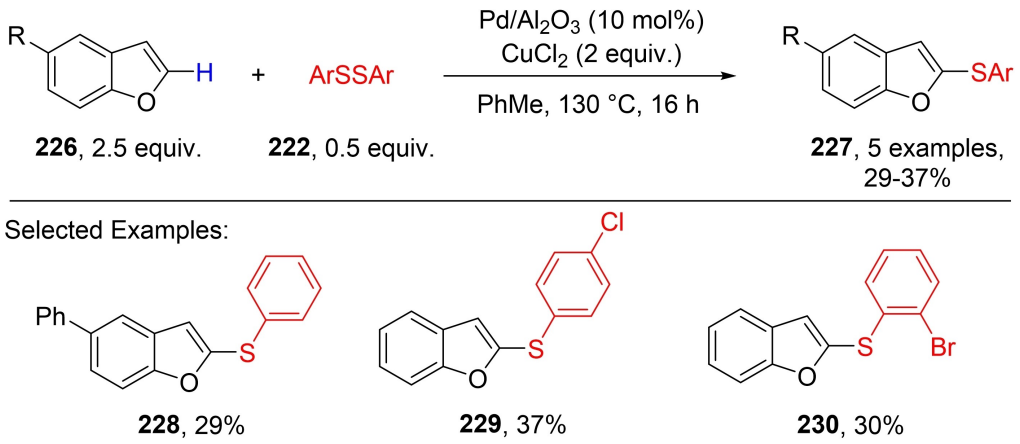


Scheme 51. Cu-catalysed C3-phosphonation of benzofurans and benzothiophenes.

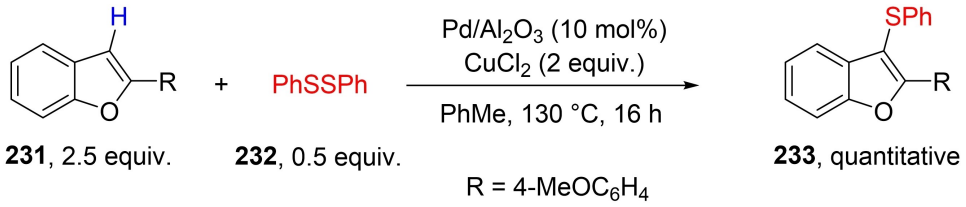


Scheme 52. C3-phenylthiolation of benzothiophenes.

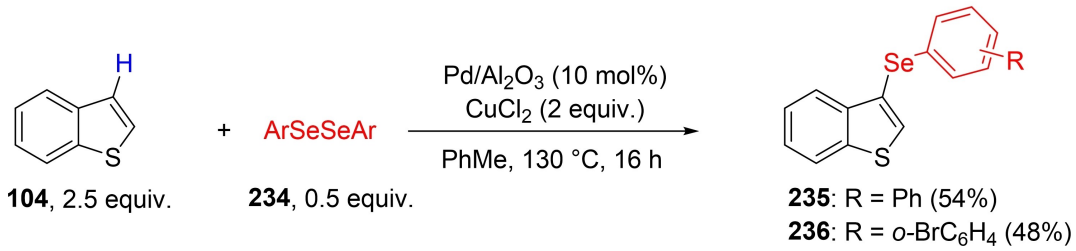
Duñach *et al.* recently developed the C–H carbamoylation of heteroaromatics, including examples of benzofuran and benzothiophene, using lewis acid-activated carbamoyl chlorides **248**.[44] Trimethylsilyl triflate (TMSOTf) was found to be the most efficacious Lewis acid, with the *in situ* generation of the highly electrophilic carbamoyl triflate species **249** (Scheme 58) confirmed by NMR studies.



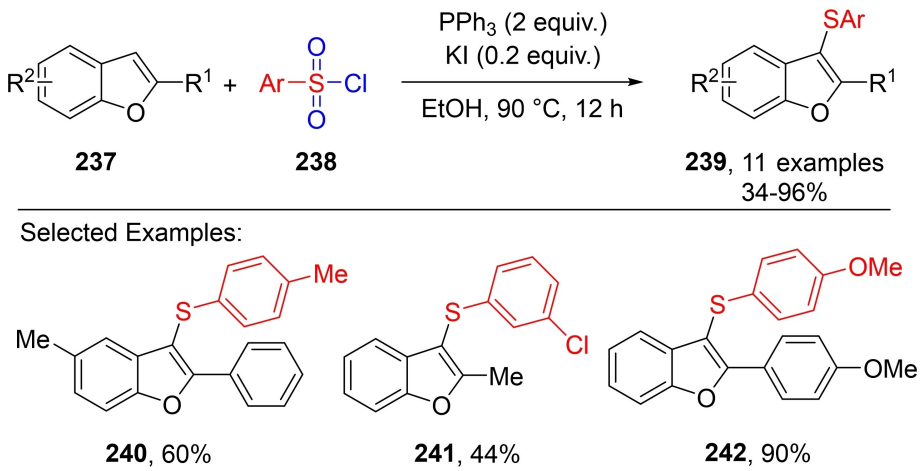
Scheme 53. C2-phenylthiolation of benzofurans.



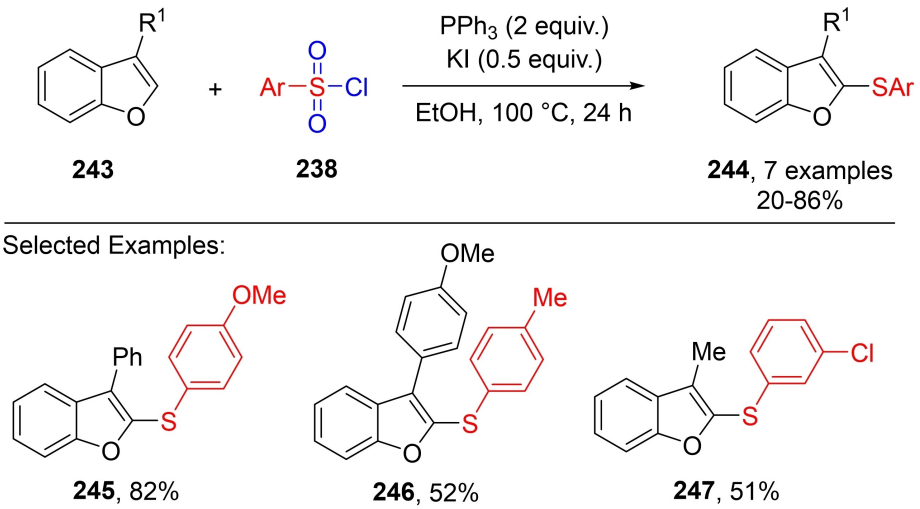
Scheme 54. C3-phenylthiolation of benzofurans.



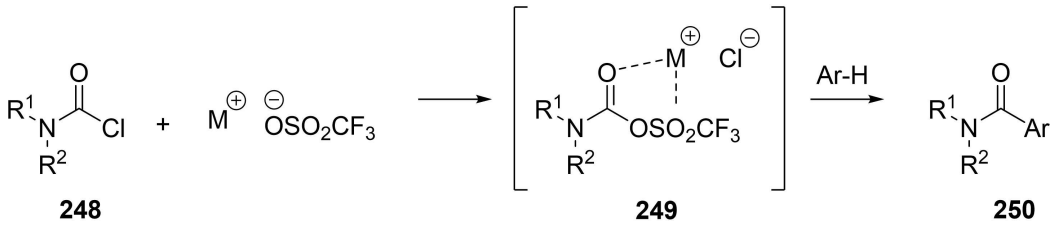
Scheme 55. C3-phenylselenation of benzothiophene.



Scheme 56. Iodide promoted C3-phenylthiolation of benzofurans.



Scheme 57. Potassium iodide promoted C2-phenylthiolation of benzofurans.



Scheme 58. Highly electrophilic carbamoyl triflate species.

The reaction proceeded in nitromethane at reflux for 3 h, giving the benzofuran and benzothiophene products **251** and **252** in 90% and 72% yields respectively (Scheme 59) For both heterocycles, the reaction showed good regioselectivity for C2-functionalisation.

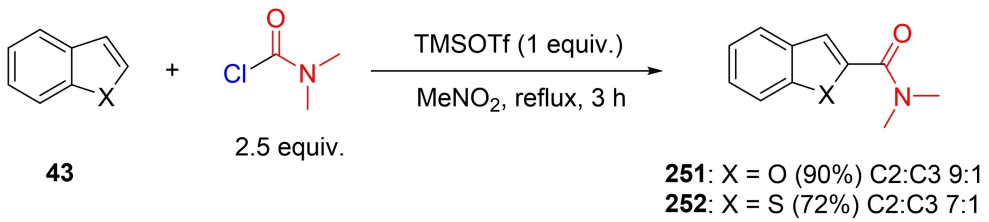
In 2016, Pilarski and co-workers reported the ruthenium catalysed silylation of aminomethyl benzofuran and benzothiophene derivatives with alkylarylsilanes.[45] Using ruthenium catalyst $RuH_2(CO)(PPh_3)_3$ with norbornene (nbe) acting as a hydrogen scavenger in toluene at 135 °C for 20 h, benzothiophene derivative **255** was obtained in 75% yield (Scheme 60).

Under the same conditions, C3-silylated benzofuran **257** was formed in a reduced yield of 25% (Scheme 61).

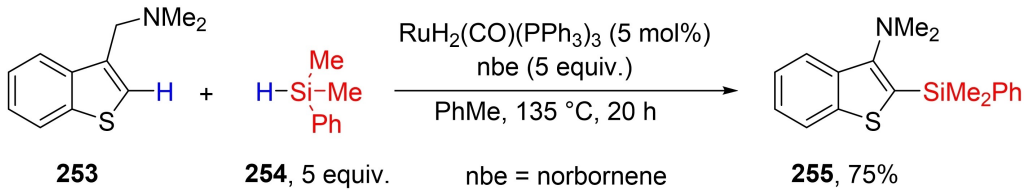
In slightly altered reaction conditions using 10 equiv. of nbe and heating at 150 °C, undirected silylation was possible and yielded benzofuran **259** in 90% yield with complete regioselectivity for the C2-position (Scheme 62).

König *et al.* have recently reported the redox-neutral photocatalytic carboxylation of a range of arenes and styrenes using the photoreductant 2,3,6,7-tetramethoxyanthracen-9(10H)-one (TMAH).[46] Demonstrated examples included several benzothiophenes and benzofurans (Scheme 63).

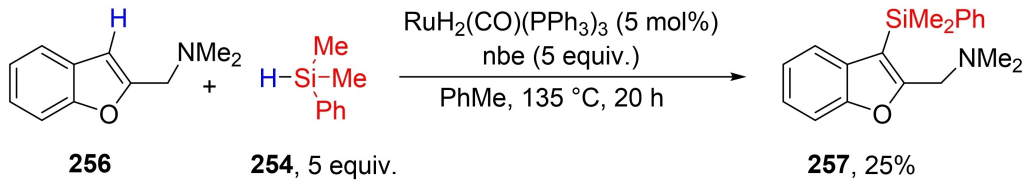
More excitingly, using the same conditions the group reported the only example of which we are aware of C–H functionalisation on the 6-member ring of a benzothiophene. Under the standard conditions, hydroxybenzothiphene **263** was carboxylated in the 7-position to give **264** in 99% yield (Scheme 64).[46]



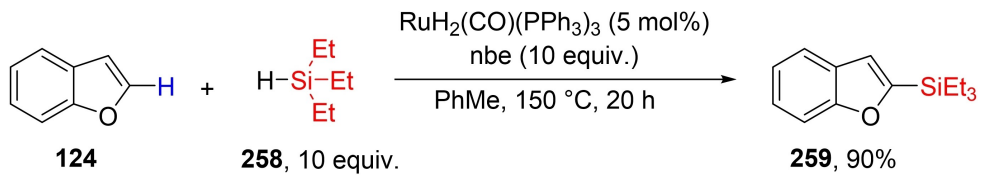
Scheme 59. Carbamoylation of benzofuran and benzothiophene.



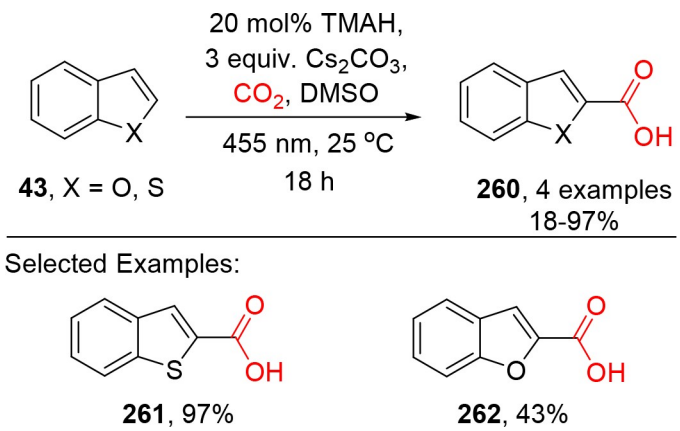
Scheme 60. Ru-catalysed directed silylation of benzothiophene.



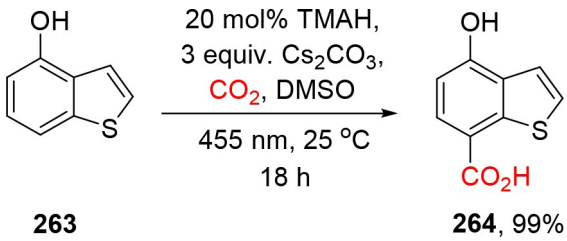
Scheme 61. Ru-catalysed directed silylation of benzofuran.



Scheme 62. Ru-catalysed undirected silylation of benzofuran.



Scheme 63. Photocatalytic carboxylation of benzothiophenes and benzofurans.



Scheme 64. C-7 carboxylation of benzothiophene **263**.

5. Intermolecular Cyclisations

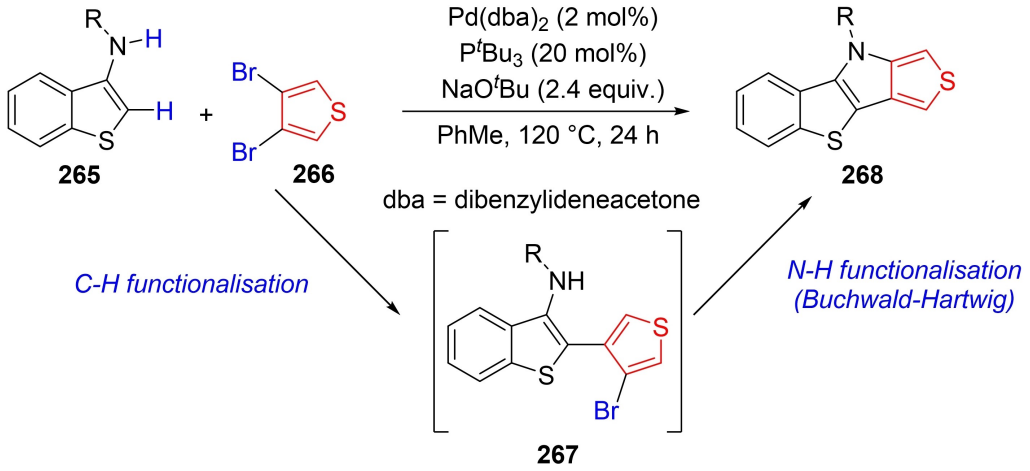
Finally, there have also been a number of intermolecular cyclizations reported recently that harness C–H functionalisation of benzofurans and benzothiophenes. In 2015, the Waldvogel group reported the Pd-catalysed domino C–H/N–H functionalisation of benzothiophene derivatives **265**.[47] Mechanistic studies showed that the C–H functionalisation occurred first, followed by the N–H functionalisation to give **268** (Scheme 65).

Using 3,4-dibromothiophene **266** and a $Pd(dba)_2/P^tBu_3$ catalyst with a NaO^tBu base, the reaction proceeded in toluene at 120 °C for 24 h, giving the desired products in good yields of **268** between 32–73% (Scheme 66). However, only aryl-substituted amines were found to be amenable to reaction, with *N*-alkyl amines not giving rise to the desired products.

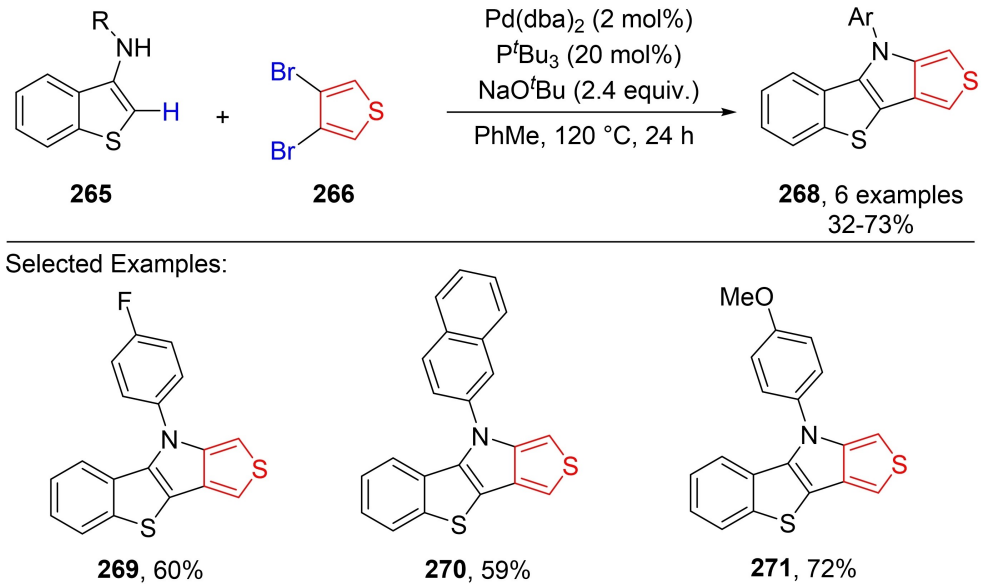
Additionally, the reaction worked with *o*-dibromoarenes **272** as the coupling partner under the same conditions giving products **273** in excellent yields up to 86% (Scheme 67).

Kuninobu and co-workers have described a Pd-catalysed intermolecular cyclization *via* oxidative C–H/C–H coupling of heterocyclic derivatives **277** including benzofurans and benzothiophenes.[48] Using the catalyst $[Pd(OPiv)_2]$ with oxidant AgOPiv in DMF heated at 150 °C for 48 h, a range of coupled products **278** bearing different heterocyclic linkages were generated in good yields of 42–85% (Scheme 68).

This protocol was also applied to compounds **282** bearing two benzothiophene groups with oxygen linkages, and utilising



Scheme 65. Pd-catalysed domino C–H/N–H functionalisation of benzothiophene derivatives.



Scheme 66. C–H/N–H functionalisation of benzothiophene derivatives with 3,4-dibromothiophene.

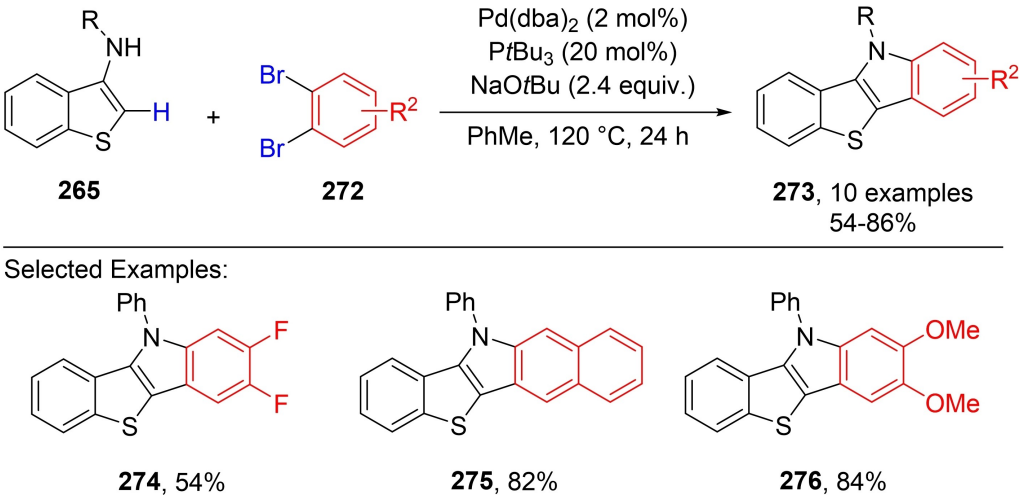
higher catalyst loading, and larger equivalents of oxidant yielded the extended π-conjugated product **283** in 62% yield (Scheme 69).

In 2016, the Kim group utilised the Pd-catalysed intermolecular cyclization of benzofurans to access pterocarpene and coumestan precursors.[49] Using $Pd(OAc)_2$, with tetra-*n*-butylammonium bromide (TBAB) and potassium acetate in DMF at 100 °C for 12 h, cyclised products **285** were obtained in excellent yields of 62–95% (Scheme 70). These compounds could then be easily oxidised with DDQ at the benzylic position to access the corresponding pterocarpene/coumestan derivatives.

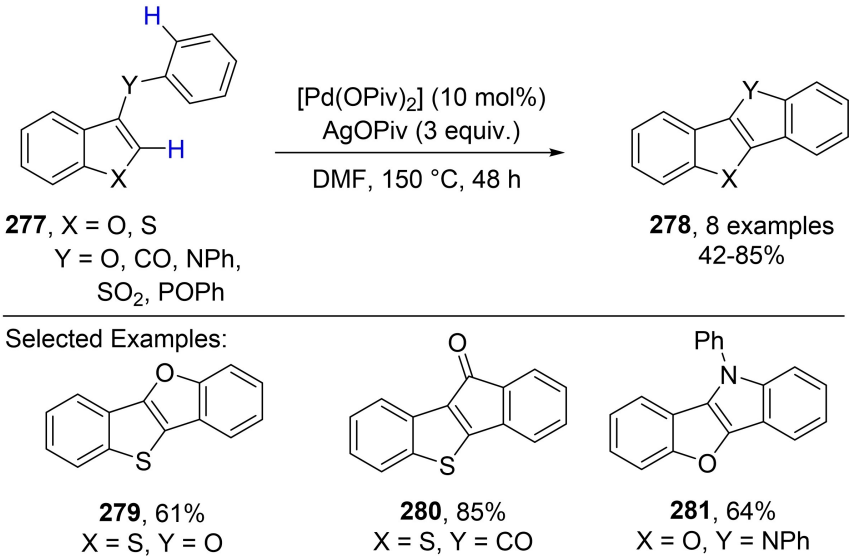
More recently, Saura-Llamas and co-workers investigated the cyclopalladation of benzofuran and benzothiophene derivatives **288** bearing ethylamine at the C3 position (Scheme 71).[50] The resulting palladacycles **289** were then subject to Pd–C insertions with a variety of coupling partners.

Firstly, the group investigated the insertion of isocyanides into the Pd–C bond. For the benzofuran palladacycle **290**, insertion of trimethylacetonitrile was achieved simply through heating in toluene at 120 °C for 18 h to afford amidinium salt **291** in 29% yield. Whilst for the benzothiophene equivalent substrate **292**, the reaction proceeded upon addition of silver triflate and stirring in chloroform at room temperature for 24 h before heating to reflux for 3 days giving **293** in 50% yield (Scheme 72).

Carbon monoxide could also be inserted into these Pd–C bonds to give the corresponding lactams. The benzofuran lactam **295** was constructed in 27% yield from the corresponding palladacycle **294** after stirring overnight in chloroform in a carbon monoxide environment in the presence of triethylamine.



Scheme 67. C–H/N–H functionalisation of benzothiophene derivatives with *o*-dibromoarenes.



Scheme 68. Pd-catalysed intermolecular cyclization via an oxidative C–H/C–H coupling.

Meanwhile, the benzothiophene equivalent **296** required heating at 65 °C to give lactam **297** in 54% yield (Scheme 73).

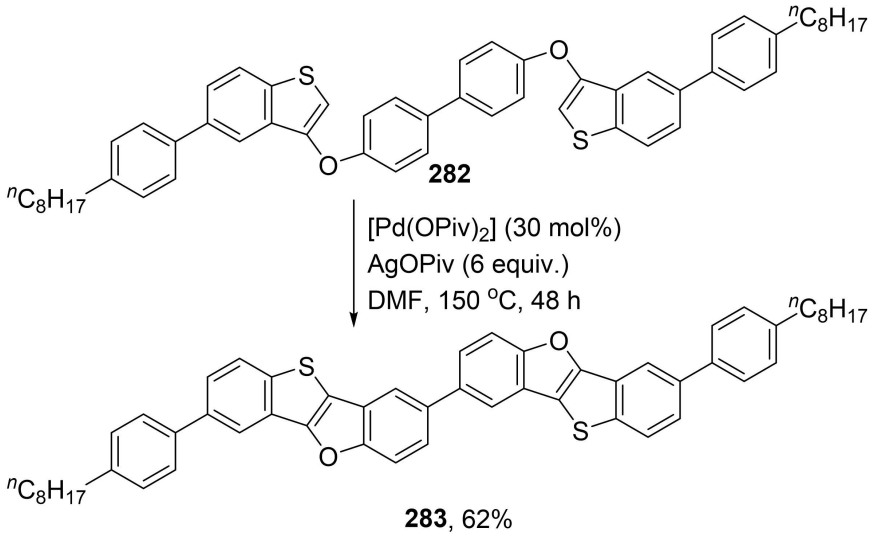
C–H alkenylation was achieved by insertion of methyl acrylate into the Pd–C bond, giving benzofuran **298** and benzothiophene **299** alkenes in 28% and 58% yields respectively, both with stereoselectivity of 2:1 in favour of the *E* isomer. The benzofuran alkene was formed after heating to 65 °C in chloroform overnight, whilst the benzothiophene first required the addition of silver triflate in acetone at room temperature overnight, before a solvent swap and being subject to the previous conditions for 48 h (Scheme 74).

While nitrile and CO insertions were only demonstrated using stoichiometric palladium, C–H alkenylation could be carried out using catalytic palladium. $Pd(OAc)_2$, with $Cu(OAc)_2$ oxidant, and methyl acrylate was refluxed in 1,2-dichloroethane (DCE) for 16 h, giving benzofuran **301** in 77% yield. Benzothiophene derivative **302** was produced in 57% yield, under the altered conditions of acetonitrile heated at 110 °C for 48 h (Scheme 75).

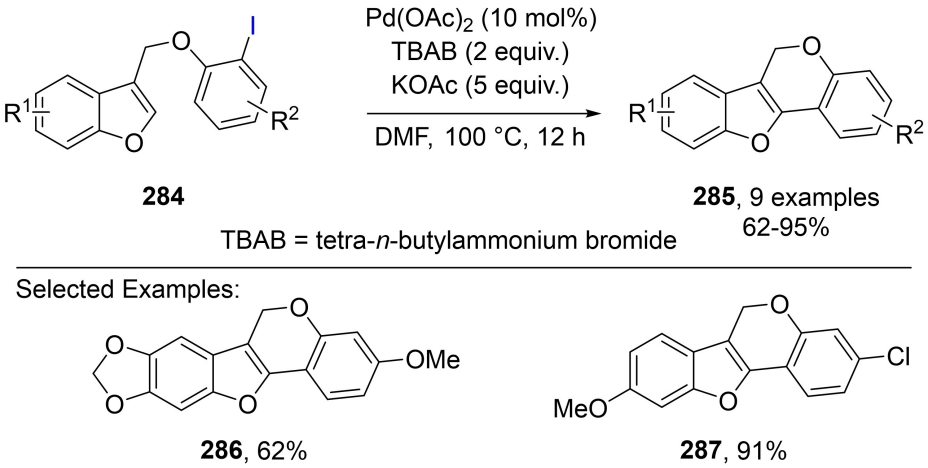
6. Conclusions/perspectives

Recent advances in the C–H functionalisation of benzofuran and benzothiophene have been described in this review. A broad range of functionality can be installed onto the heterocycles by formation of C–C bonds through arylation, alkenylation, alkylation, carbomoylation, and annulations. Additionally, borylation, silylation, thiolation, selenation, and phosphoration have been investigated to form bonds other than C–C.

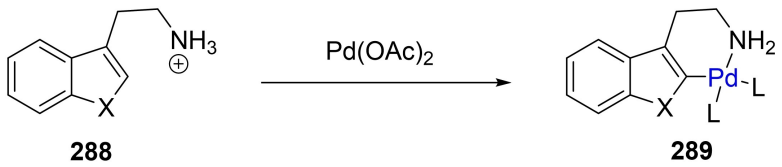
Despite the considerable improvements to the functionalisation of benzofurans and benzothiophenes over the past



Scheme 69. Synthesis of π-conjugated product via Pd-catalysed intermolecular cyclization.



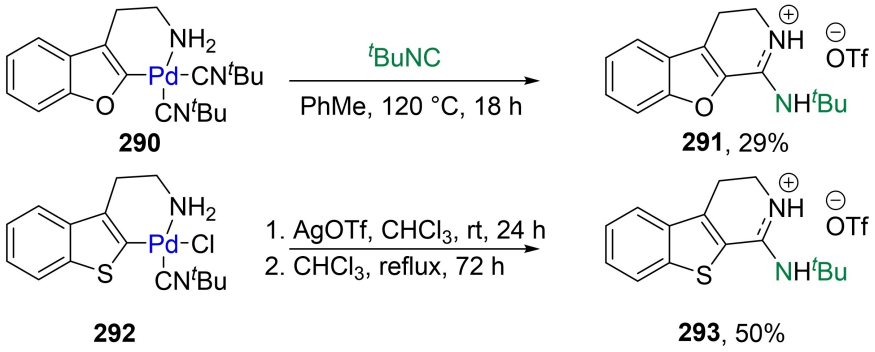
Scheme 70. Pterocarpene/coumestan precursor synthesis employing Pd-catalysed intermolecular cyclisation.



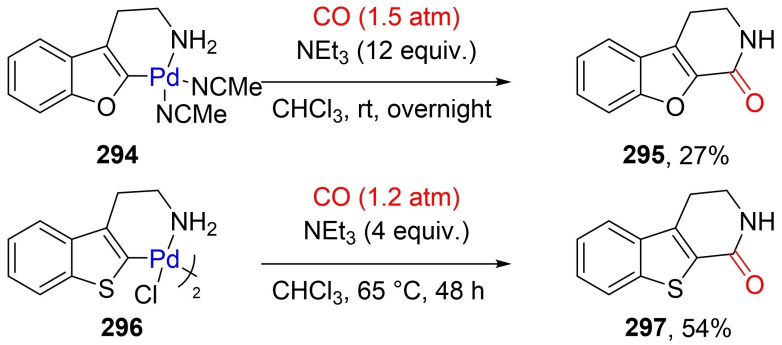
Scheme 71. Palladation of benzofurans and benzothiophene derivatives.

5 years, there remain some inherent issues yet to be resolved. For example, the Proctor group's use of benzothiophene *S*-oxides to enable access alkylated benzothiophene products is an exciting development,[24] however this cannot be applied to access alkylated benzofurans. Developments here would have practical use in the development of small-molecule drugs like the benzofuranyloxoacetic acid EPAC1-selective activators, where changing the alkyl C3-substituent was shown to alter both EPAC selectivity and potency.[7]

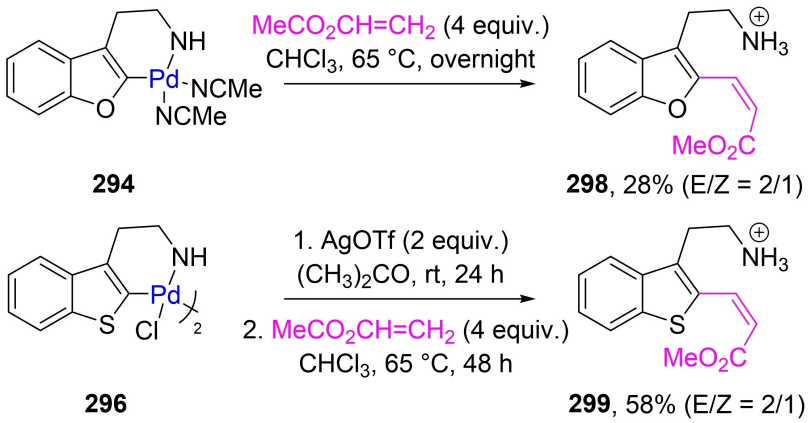
Additionally, many of the C–H functionalisation protocols described either focus solely on one heterocycle or have a single example highlighting the practicality of the other heterocycle. More expansive methodologies encompassing both benzofuran and benzothiophenes as well as other heterocycles would be a useful tool for organic chemists. The direct C–H functionalisation of positions other than C2/C3 remains unexplored; although clearly challenging, advancements in this area could provide routes to previously unexplored chemical space



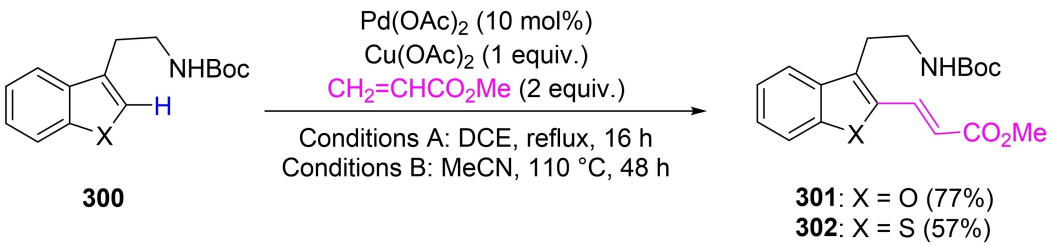
Scheme 72. Isocyanide insertion of benzofuran/benzothiophene palladacycles.



Scheme 73. Carbon monoxide insertion of benzofuran/benzothiophene palladacycles.



Scheme 74. Methyl acrylate insertion into benzofuran/benzothiophene palladacycles.



Scheme 75. Pd-catalysed alkenylation of Boc-protected 3-aminobenzofuran and benzothiophene derivatives.

in the synthesis of analogous drug molecules. Finally, engagement with continuous flow chemistry remains low across the C–H functionalisation field. We propose that greater uptake of this technology will have considerable efficiency and safety benefits during scale-up of benzofuran and benzothiophene C–H functionalisations in future drug manufacture.

Conflict of Interest

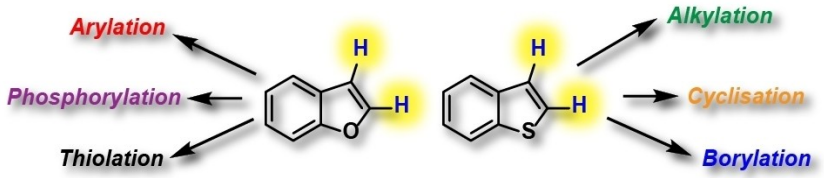
The authors declare no conflict of interest.

Keywords: Benzofuran · Benzothiophene · Functionalization · Heterocycles · Synthetic methods

[1] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859.
[2] S. De Leo, L. E. Braverman, in *The Thyroid and Its Diseases: A Comprehensive Guide for the Clinician*, 1st ed. (Eds.: M. Luster, L. H. Duntas, L. Wartofsky), Springer International Publishing, Cham, **2019**, pp. 417–433.
[3] P. E. Mouli, T. Selvakumar, S. Kumar, S. Parthiban, R. Priya, M. Deivanayagi, *Int. J. Nutr.* **2013**, *3*, 229–235.
[4] J. D. Croxtall, G. L. Plosker, *Drugs* **2009**, *69*, 339–359.
[5] P. Lu, M. L. Schrag, D. E. Slaughter, C. E. Raab, M. Shou, A. D. Rodrigues, *Drug Metab. Dispos.* **2003**, *31*, 1352–1360.
[6] D. Clemett, C. M. Spencer, *Drugs* **2000**, *60*, 379–411.
[7] E. M. Beck, E. Parnell, A. Cowley, A. Porter, J. Gillespie, J. Robinson, L. Robinson, A. D. Pannifer, V. Hamon, P. Jones, A. Morrison, S. McElroy, M. Timmerman, H. Rutjes, P. Mahajan, J. Wiejak, U. Luchowska-Stańska, D. Morgan, G. Barker, H. Rehmann, S. J. Yarwood, *Cells* **2019**, *8*, 1425–1443.
[8] a) Y.-h. Miao, Y.-h. Hu, J. Yang, T. Liu, J. Sun, X.-j. Wang, *RSC Adv.* **2019**, *9*, 27510–27540; b) Majid M. Heravi, V. Zadsirjan, H. Hamidi, P. H. Tabar A-miri, *RSC Adv.* **2017**, *7*, 24470–24521.
[9] a) R. S. Keri, K. Chand, S. Budagumpi, S. Balappa Somappa, S. A. Patil, B. M. Nagaraja, *Eur. J. Med. Chem.* **2017**, *138*, 1002–1033; b) D. Goyal, A. Kaur, B. Goyal, *ChemMedChem* **2018**, *13*, 1275–1299.
[10] a) S. Agasti, A. Dey, D. Maiti, *Chem. Commun.* **2017**, *53*, 6544–6556; b) A. S. Dudnik, G. V., in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: Y. A. K.), Wiley-VCH, New York, **2010**.
[11] S. El Kazzouli, J. Koubachi, N. El Brahmi, G. Guillaumet, *RSC Adv.* **2015**, *5*, 15292–15327.
[12] Y. Mohr, G. Hisler, L. Grousset, Y. Roux, E. A. Quadrelli, F. M. Wisser, J. Canivet, *Green Chem.* **2020**, *22*, 3155–3161.
[13] H. P. L. Gemoets, I. Kalvet, A. V. Nyuchev, N. Erdmann, V. Hessel, F. Schoenebeck, T. Noël, *Chem. Sci.* **2017**, *8*, 1046–1055.
[14] a) C. S. Bryan, J. A. Braunger, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 7064–7068; *Angew. Chem.* **2009**, *121*, 7198–7202; b) B. Gabriele, R. Mancuso, E. Lupinacci, L. Veltri, G. Salerno, C. Carfagna, *J. Org. Chem.* **2011**, *76*, 8277–8286; c) S. Uchida, H. Kinoshita, K. Miura, *Org. Lett.* **2020**, *22*, 3123–3127; d) L.-L. Sun, C.-L. Deng, R.-Y. Tang, X.-G. Zhang, *J. Org. Chem.* **2011**, *76*, 7546–7550; e) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680; f) K. C. Nicolaou, S. A. Snyder, A. Bigot, J. A. Pfefferkorn, *Angew. Chem. Int. Ed.* **2000**, *39*, 1093–1096; *Angew. Chem.* **2000**, *112*, 1135–1138.
[15] K. Srinivas, S. K. Siddiqui, J. K. Mudaliar, C. V. Ramana, *J. Org. Chem.* **2019**, *84*, 5056–5066.
[16] H. Zhang, S. Li, Q. Kang, Y. Du, *Org. Chem. Front.* **2019**, *6*, 3683–3687.
[17] C. Theunissen, J. Wang, G. Evano, *Chem. Sci.* **2017**, *8*, 3465–3470.
[18] Y. Yamane, K. Yoshinaga, M. Sumimoto, T. Nishikata, *ACS Catal.* **2019**, *9*, 1757–1762.
[19] G. Xu, K. Liu, J. Sun, *Org. Lett.* **2018**, *20*, 72–75.
[20] W.-F. Tian, C.-H. Hu, K.-H. He, X.-Y. He, Y. Li, *Org. Lett.* **2019**, *21*, 6930–6935.
[21] M. T. Westwood, C. J. C. Lamb, D. R. Sutherland, A.-L. Lee, *Org. Lett.* **2019**, *21*, 7119–7123.
[22] A. Lerchen, T. Knecht, M. Koy, J. B. Ernst, K. Bergander, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 15248–15252.
[23] S. Barik, S. Shee, A. Ghosh, A. T. Biju, *Org. Lett.* **2020**, *22*, 3865–3869.
[24] a) Z. He, H. J. Shrives, J. A. Fernández-Salas, A. Abengózar, J. Neufeld, K. Yang, A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2018**, *57*, 5759–5764; *Angew. Chem.* **2018**, *130*, 5861–5866; b) H. J. Shrives, J. A. Fernández-Salas, C. Hedtke, A. P. Pulis, D. J. Procter, *Nat. Commun.* **2017**, *8*, 14801.
[25] L. H. S. Smith, S. C. Coote, H. F. Sneddon, D. J. Procter, *Angew. Chem. Int. Ed.* **2010**, *49*, 5832–5844; *Angew. Chem.* **2010**, *122*, 5968–5980.
[26] J. Cao, Z.-L. Chen, S.-M. Li, G.-F. Zhu, Y.-Y. Yang, C. Wang, W.-Z. Chen, J.-T. Wang, J.-Q. Zhang, L. Tang, *Eur. J. Org. Chem.* **2018**, *2018*, 2774–2779.
[27] P. Saxena, N. Maida, M. Kapur, *Chem. Commun.* **2019**, *55*, 11187–11190.
[28] X. Yu, Z. Huang, W. Liu, S. Shi, C. Kuang, *Org. Biomol. Chem.* **2015**, *13*, 4459–4465.
[29] W. Hagui, N. Besbes, E. Srasra, J.-F. Soulé, H. Doucet, *RSC Adv.* **2016**, *6*, 17110–17117.
[30] B. S. Cho, Y. K. Chung, *Chem. Commun.* **2015**, *51*, 14543–14546.
[31] Y. Wu, W. Li, L. Jiang, L. Zhang, J. Lan, J. You, *Chem. Sci.* **2018**, *9*, 6878–6882.
[32] a) J.-H. Chu, P.-S. Lin, M.-J. Wu, *Organometallics* **2010**, *29*, 4058–4065; b) L. Ackermann, E. Diers, A. Manvar, *Org. Lett.* **2012**, *14*, 1154–1157.
[33] Z. Wang, F. Wang, Z. Liu, S. He, X. Pu, Y. Yang, G. Gao, *Chem. Commun.* **2019**, *55*, 10599–10602.
[34] G. Tan, Q. You, J. You, *ACS Catal.* **2018**, *8*, 8709–8714.
[35] T. Doba, T. Matsubara, L. Ilies, R. Shang, E. Nakamura, *Nat. Can.* **2019**, *2*, 400–406.
[36] R. Padmavathi, R. Sankar, B. Gopalakrishnan, R. Parella, S. A. Babu, *Eur. J. Org. Chem.* **2015**, *2015*, 3727–3742.
[37] D. J. Paymode, C. V. Ramana, *J. Org. Chem.* **2015**, *80*, 11551–11558.
[38] E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60*, 3020–3027.
[39] A. J. Cresswell, G. C. Lloyd-Jones, *Chem. Eur. J.* **2016**, *22*, 12641–12645.
[40] R. Shishido, I. Sasaki, T. Seki, T. Ishiyama, H. Ito, *Chem. Eur. J.* **2019**, *25*, 12924–12928.
[41] Y. Wang, Y. Yang, K. Jie, L. Huang, S. Guo, H. Cai, *ChemCatChem* **2018**, *10*, 716–719.
[42] S. Vásquez-Céspedes, A. Ferry, L. Candish, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 5772–5776; *Angew. Chem.* **2015**, *127*, 5864–5868.
[43] X. Zhao, X. Lu, A. Wei, X. Jia, J. Chen, K. Lu, *Tetrahedron Lett.* **2016**, *57*, 5330–5333.
[44] A. Uehara, S. Olivero, B. Michelet, A. Martin-Mingot, S. Thibaudeau, E. Duñach, *Eur. J. Org. Chem.* **2019**, *2019*, 46–49.
[45] K. Devaraj, C. Sollert, C. Juds, P. J. Gates, L. T. Pilarski, *Chem. Commun.* **2016**, *52*, 5868–5871.
[46] M. Schmalzbauer, T. D. Svejstrup, F. Fricke, P. Brandt, M. J. Johansson, G. Bergonzini, B. König, *Chem* **2020**, *6*, 2658–2672.
[47] N. Kamimoto, D. Schollmeyer, K. Mitsudo, S. Suga, S. R. Waldvogel, *Chem. Eur. J.* **2015**, *21*, 8257–8261.
[48] K. Saito, P. K. Chikkade, M. Kanai, Y. Kuninobu, *Chem. Eur. J.* **2015**, *21*, 8365–8368.
[49] M. Nayak, Y. Jung, I. Kim, *Org. Biomol. Chem.* **2016**, *14*, 8074–8087.
[50] M. Pérez-Gómez, S. Hernández-Ponte, J. A. García-López, R. Frutos-Pedreño, D. Bautista, I. Saura-Llamas, J. Vicente, *Organometallics* **2018**, *37*, 4648–4663.

Manuscript received: November 9, 2020
Revised manuscript received: December 3, 2020
Accepted manuscript online: December 4, 2020

MINIREVIEWS



In this review, we summarise progress in benzofuran and benzothiophene C–H functionalisations over the past five years, including 1) alkylations, 2) arylations and heteroarylations, 3) carboxylations, carbamoylations and C-heteroatom bond formations and 4) cyclisations.